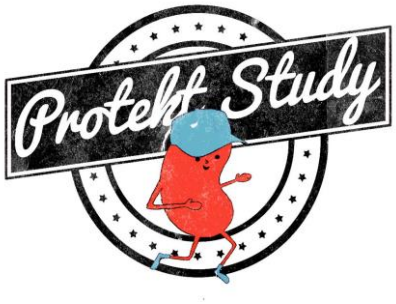
CTRC
Clinical Trials Research Centre



PROteKT (Phase IIa, Randomised, Controlled, Open-Label Trial of Rosuvastatin for the Prevention of Aminoglycoside-Induced Kidney Toxicity in Children with Cystic Fibrosis)

Eudract No. 2014-002387-32

Final Analysis Report v2.0

	ORIGINATED BY	QC PERFORMED BY	APPROVED BY
Name	Anna Rosala-Hallas	Barbara Arch	Ashley Jones
Title	Trial Statistician	QC statistician	Lead statistician
Date	04/07/2018		
Protocol Version and Date	Version 8.0 on 06/02/2017		

Change Control

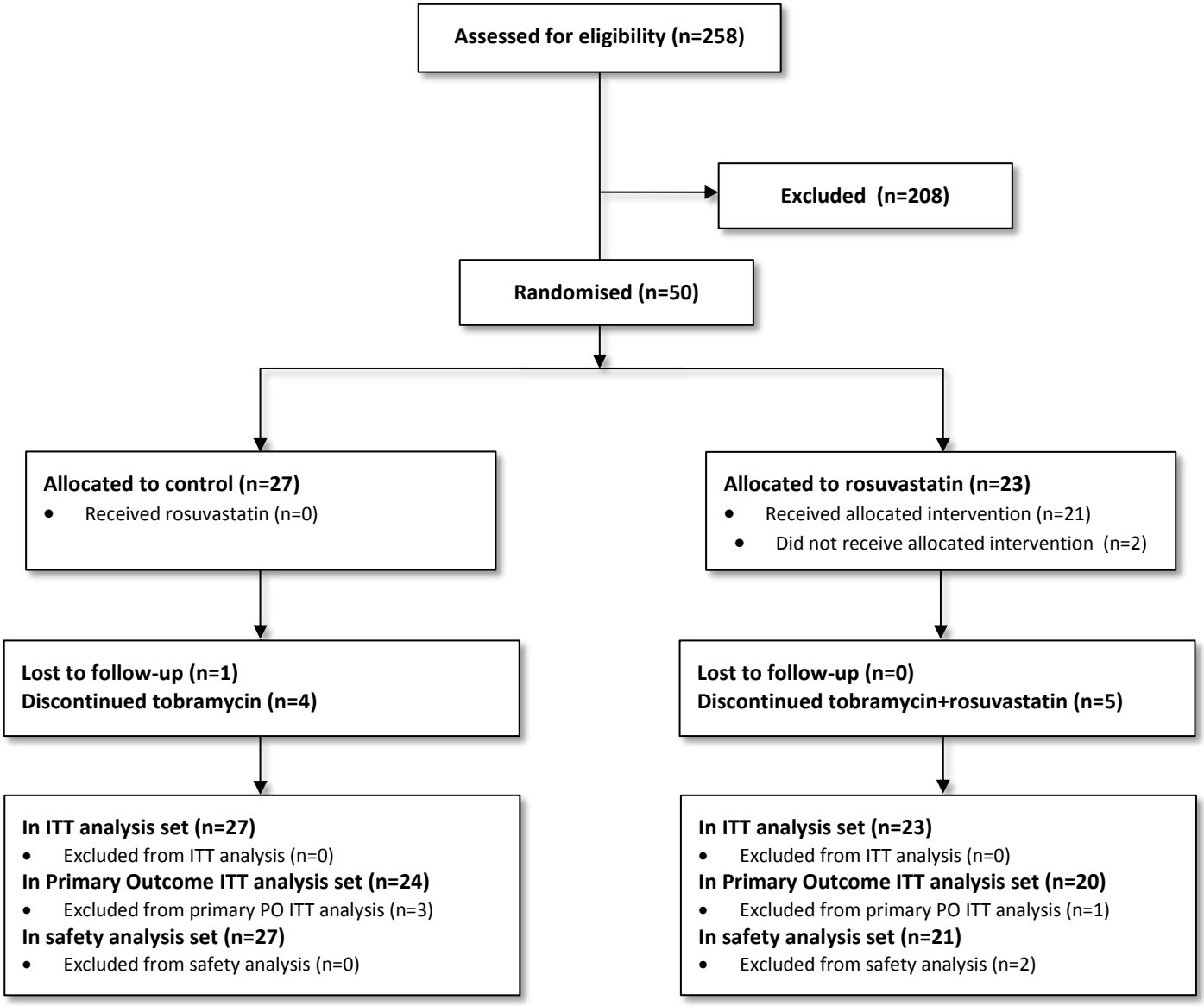
Updated report version no.	Section changed	Description of change	Date changed	Initials
2	8	Normalised KIM-1 and NGAL values have been converted from (pg/ml)/(mg/dl) to ng/mgCr.	04/07/2018	ARH
2	8.1.8	Incorrect references to creatinine replaced with eGFR in text	11/10/2018	ARH
2	8.1.9	Incorrect references to creatinine replaced with NGAL in text	11/10/2018	ARH
2	8.1.9.3	95% confidence interval updated to correct typos	11/10/2018	ARH
2	9	Addition of post-hoc analyses (appended from Post-hoc report v1.0)	04/07/2018	ARH
2	9.3	Addition of mean profile plots for normalised KIM-1	04/07/2018	ARH
2	9.10	Addition of KIM-1 and NGAL reference levels (Post-hoc)	04/07/2018	ARH
2	9.11	Addition of Serum creatinine increases from baseline (Post-hoc)	04/07/2018	ARH
2	9.12	Addition of Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin (Post-hoc)	04/07/2018	ARH

1. Table of Contents

2. List of Tables and Figures

3. CONSORT diagram

Figure 3.1: CONSORT diagram



4. Randomisation checking

Table 4.1: Summary of randomisation problems

Site	Problem	Action(s) taken
00248 - Sheffield Children's Hospital	The 9th participant randomised was the first recruit from Sheffield. The participant was randomised to the correct allocation but had been given the incorrect randomisation number 00248001 as opposed to 00248009, as randomisation numbers in this trial are allocated across sites rather than in site. This was due to an older version of the code being used when IS programmer implemented a change of text for exclusion criteria.	• The live randomisation system was temporarily taken offline and sites notified to contact the trial coordinator. • The backup of the live system was reinstated to the test system location. • The test system underwent full regression tests. • When those tests passed the test system was made the live system. • An incident report was produced.
14570 - Nottingham Children's Hospital	Due to temporary halt in live randomisation system described above, a back-up envelope was used for the second recruit in Nottingham.	• No action needed.

5. Recruitment

Table 5.1: Screening summary by site

Site	Date of site opening	Screenings [a] (independent screenings)	Eligible [b] (% of [a])	Ineligible (% of [a])	Eligible and consent [c] (% of [b])	Eligible no consent (% of [b])	Consented not randomised (% of [c])	Randomised (% of [c])
00243 - Alder Hey Children's Hospital	14-May-15	34 (32)	8 (23.53%)	26 (76.47%)	2 (25.00%)	6 (75.00%)	0 (0.00%)	2 (100%)
00116 - Bristol Royal Hospital for Children	15-May-15	42 (41)	16 (38.10%)	26 (61.90%)	5 (31.25%)	10 (62.50%)	0 (0.00%)	5 (100%)
14570 - Nottingham Children's Hospital	15-May-15	47 (47)	14 (29.79%)	33 (70.21%)	10 (71.43%)	4 (28.57%)	1 (10.00%)	9 (90.00%)
00161 - King's College Hospital	21-May-15	11 (11)	5 (45.45%)	6 (54.55%)	3 (60.00%)	2 (40.00%)	0 (0.00%)	3 (100%)
00248 - Sheffield Children's Hospital	21-May-15	21 (15)	17 (80.95%)	4 (19.05%)	5 (29.41%)	11 (64.71%)	0 (0.00%)	5 (100%)
00249 - Great Ormond Street Hospital	27-May-15	25 (25)	15 (60.00%)	9 (36.00%)	7 (46.67%)	8 (53.33%)	0 (0.00%)	7 (100%)
00031 - Leicester Royal Infirmary	10-Nov-15	32 (32)	14 (43.75%)	18 (56.25%)	5 (35.71%)	9 (64.29%)	0 (0.00%)	5 (100%)
00182 - University Hospital North Midlands	17-Nov-15	20 (20)	20 (100%)	0 (0.00%)	7 (35.00%)	13 (65.00%)	0 (0.00%)	7 (100%)
09888 - Royal Alexandra Children's Hospital	11-Feb-16	13 (13)	7 (53.85%)	6 (46.15%)	1 (14.29%)	6 (85.71%)	0 (0.00%)	1 (100%)
00083 - Countess of Chester Hospital	19-Apr-16	4 (4)	2 (50.00%)	2 (50.00%)	1 (50.00%)	1 (50.00%)	0 (0.00%)	1 (100%)
00002 - Royal Devon and Exeter	06-May-16	7 (7)	5 (71.43%)	2 (28.57%)	3 (60.00%)	2 (40.00%)	0 (0.00%)	3 (100%)
13258 – Norfolk and Norwich University Hospital	29-Sep-16	7 (7)	1 (14.29%)	6 (85.71%)	1 (100%)	0 (0.00%)	1 (100%)	0 (0.00%)
00133 – Birmingham Children's Hospital	04-Oct-16	4 (4)	2 (50.00%)	2 (50.00%)	2 (100%)	0 (0.00%)	0 (0.00%)	2 (100%)
	Total	267 (258)	126[1] (47.19%)	140 (52.43%)	52[2] (41.27%)	72 (57.14%)	2 (3.85%)	50 (96.15%)

[1]One participant had eligibility status unknown – consent was declined; [2]Two participants had consent status unknown.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis - Screening.sas*

Table 5.2: Reason(s) for ineligibility

Reason	N	% of 140
Participant not within the required age range[1]	48	34%
Patient is no longer being considered for Tobramycin treatment	60	43%
Participant taking excluded con med (see protocol)	7	5%
Pre-amendment: Participant did not have 7 days to read PISC	4	3%
Participant of Asian ancestry (Japanese, Chinese, Filipino, Vietnamese or Korean)	3	2%
Non-compliance	2	1%
Participant with current elevation in transaminases exceeding 3 x ULN	2	1%
Based on psychological assessment	2	1%
Awaiting liver transplant	2	1%
Participant with renal disease (eGFR<60ml/min/1.73m^2, in the 6 months preceding screening)	1	1%
Allergy to tobramycin	1	1%
CF joint pains	1	1%
Complex situation	1	1%
Female participant who is pregnant or lactating (or refusal of a pregnancy test if of child bearing potential)	1	1%
Inappropriate timing	1	1%
Not an inpatient	1	1%
Not appropriate due to social issues	1	1%
Other illness	1	1%
Previous randomisation in PROteKT	1	1%
Study information not given in enough time	1	1%
Unable to meet study requirements	1	1%
Weekend admission	1	1%
Unknown	1	1%
	144	**-**

[1]Inclusion criteria changed from 10-18 to 6-18 in protocol version 7.

Table 5.3: Reasons for non-consent

Reason	N	% of 72
Does not want to consent (unwilling to provide reason)	24	33%
Unwilling/unable to comply with study requirements	14	19%
Admitted too late	9	13%
Not given information in time	5	7%
Research team not informed	3	4%
Other medical procedures	2	3%
No research staff available	2	3%
Patient refused consent due to blood test	2	3%
Patient missed	2	3%
Acute admission	1	1%
Complex background	1	1%
Patient does not want samples taken	1	1%
Patient has diabetes	1	1%
Pre amendment: Unable to give 7 days to read PIS	1	1%
Too ill, maybe in 3 months	1	1%
Too many other commitments	1	1%
Trial medication	1	1%
Wrong aminoglycoside	1	1%
Total	**72**	**-**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis - Screening.sas*

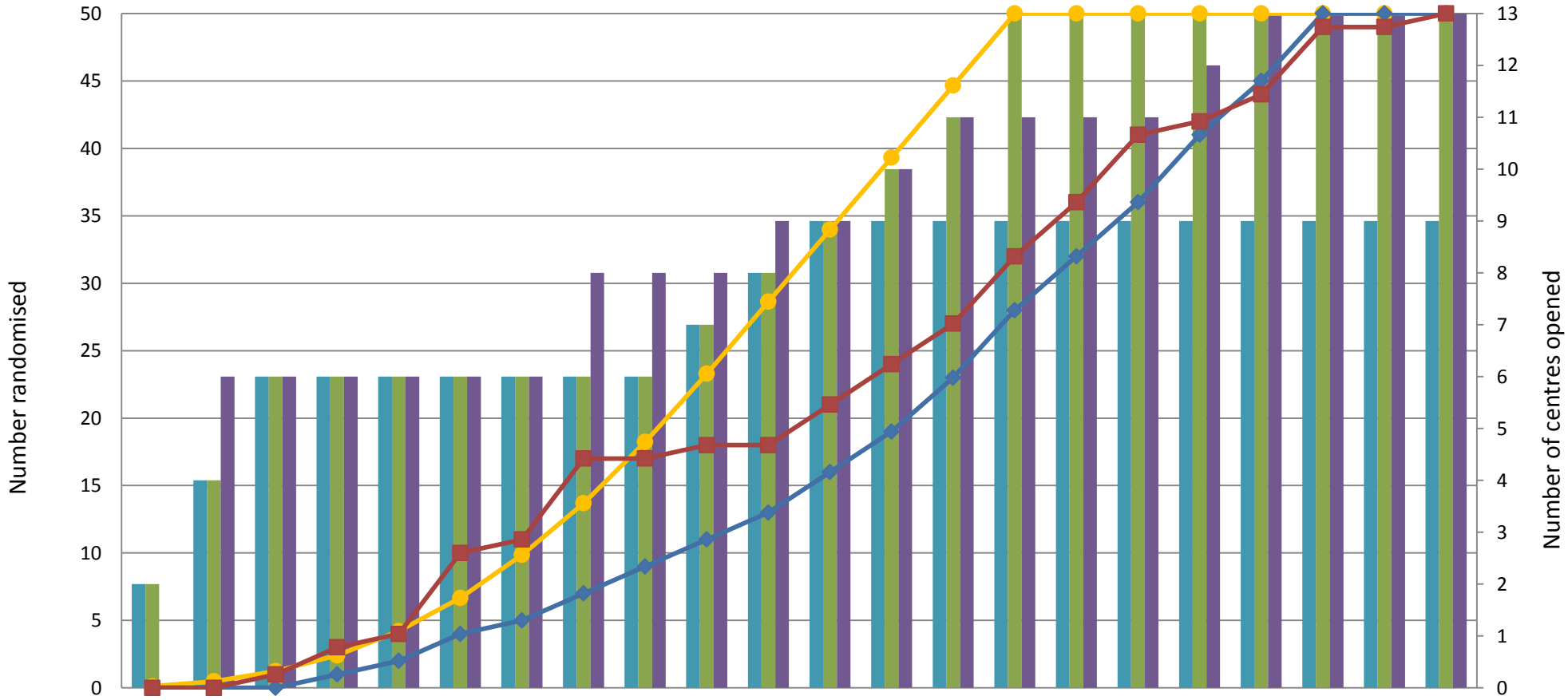
Table 5.4: Recruitment summary by site

Site	Date of site opening	Total number of months open for recruitment[1]	Number recruited[2]		
			Control	Rosuvastatin	Total
00243 - Alder Hey Children's Hospital	14-May-15	20.67	1	1	2
00116 - Bristol Royal Hospital for Children	15-May-15	20.63	3	2	5
14570 - Nottingham Children's Hospital	15-May-15	20.63	5	4	9
00161 - King's College Hospital	21-May-15	20.43	1	2	3
00248 - Sheffield Children's Hospital	21-May-15	20.43	3	2	5
00249 - Great Ormond Street Hospital	27-May-15	20.23	4	3	7
00031 - Leicester Royal Infirmary	10-Nov-15	14.67	2	3	5
00182 - University Hospital North Midlands	17-Nov-15	14.43	4	3	7
09888 - Royal Alexandra Children's Hospital	11-Feb-16	11.57	1	0	1
00083 - Countess of Chester Hospital	19-Apr-16	9.30	0	1	1
00002 - Royal Devon and Exeter	06-May-16	8.73	2	1	3
13258 – Norfolk and Norwich University Hospital	29-Sep-16	3.87	0	0	0
00133 – Birmingham Children's Hospital	04-Oct-16	3.70	1	1	2
		Total	**27**	**23**	**50**

[1]Recruitment ended on 23-Jan-2017.
[2]The 50 recruits were originally expected to come from the first 6 sites, however, due to lower recruitment rates than anticipated, a further 7 sites were opened.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis - Recruitment.sas*

Figure 5.1: Recruitment Graph



	Apr-15	May-15	Jun-15	Jul-15	Aug-15	Sep-15	Oct-15	Nov-15	Dec-15	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17
Original centres expected	2	4	6	6	6	6	6	6	6	7	8	9	9	9	9	9	9	9	9	9	9	9
Revised centres expected	2	4	6	6	6	6	6	6	6	7	8	9	10	11	13	13	13	13	13	13	13	13
Centres opened	0	6	6	6	6	6	6	8	8	8	9	9	10	11	11	11	11	12	13	13	13	13
Orginal expected	0	0	1	2	4	7	10	14	18	23	29	34	39	45	50	50	50	50	50	50	50	50
Revised expected	0	0	0	1	2	4	5	7	9	11	13	16	19	23	28	32	36	41	45	50	50	50
Actual	0	0	1	3	4	10	11	17	17	18	18	21	24	27	32	36	41	42	44	49	49	50

6. Disposition of participants

6.1 Baseline

Table 6.1: Baseline Characteristics

Baseline Characteristic	Control N=27	Rosuvastatin N=23	Total N=50
Demographic Details			
Gender, n (%)			
Male	8 (29.63%)	10 (43.48%)	18 (36.00%)
Female	19 (70.37%)	13 (56.52%)	32 (64.00%)
Missing	0	0	0
Age (years)			
Mean (SD)	13.30 (2.65)	12.09 (2.74)	12.74 (2.73)
Median (IQR)	14.22 (10.49-15.28)	11.60 (10.55-14.55)	13.03 (10.50-15.12)
Range	7.77-16.95	6.76-16.40	6.76-16.95
Missing	0	0	0
Age - EudraCT categories, n (%)			
2-11 years	8 (36%)	14 (64%)	22 (44%)
12-17 years	19 (68%)	9 (32%)	28 (56%)
Height (cm)			
Mean (SD)	151.93 (16.07)	148.43 (15.79)	150.32 (15.88)
Median (IQR)	153.80 (142.10-160.30)	147.00 (138.20-164.00)	150.65 (139.80-160.30)
Range	120.70-190.00	117.70-178.30	117.70-190.00
Missing	0	0	0
Weight (kg)			
Mean (SD)	44.67 (15.58)	40.63 (14.98)	42.81 (15.29)
Median (IQR)	42.20 (30.70-53.40)	36.10 (29.25-49.50)	40.00 (30.70-52.10)
Range	19.68-83.25	20.10-81.30	19.68-83.25
Missing	0	0	0
Ethnic origin, n (%)			
White	27 (100%	21 (91.30%)	48 (96.00%)
Other White	0 (0%)	1 (4.35%)	1 (2.00%)
Mixed: White and Black African	0 (0%)	1 (4.35%)	1 (2.00%)
Missing	0	0	0
Blood Results			
Serum creatinine (µmol/L)			
Mean (SD)	45.30 (10.56)	43.57 (11.52)	44.50 (10.94)
Median (IQR)	45.00 (37.00-53.00)	43.00 (34.00-50.00)	43.50 (36.00-50.00)
Range	30.00-66.00	28.00-75.00	28.00-75.00
Missing	0	0	0
eGFR (mL/min/1.73m^2)			
Mean (SD)	139.90 (29.69)	142.21 (27.02)	140.97 (28.23)
Median (IQR)	133.87 (118.31-154.63)	133.33 (123.56-162.59)	133.60 (122.58-161.23)
Range	95.45-198.71	95.09-212.14	95.09-212.14
Missing	0	0	0
Aspartate transaminase (iu/L)			
Mean (SD)	28.77 (11.09)	33.41 (17.69)	30.90 (14.51)
Median (IQR)	26.50 (21.00-32.00)	28.00 (23.00-38.00)	27.00 (22.00-33.00)
Range	14.00-55.00	15.00-80.00	14.00-80.00
Missing	1	1	2

Baseline Characteristic		Control N=27	Rosuvastatin N=23	Total N=50
Blood Results (cont.)				
Alanine transaminase (iu/L)				
	Mean (SD)	25.48 (16.53)	27.77 (17.09)	26.28 (16.64)
	Median (IQR)	20.00 (16.00-31.00)	22.00 (12.00-35.00)	21.00 (14.00-34.00)
	Range	10.00-82.00	9.00-62.00	9.00-82.00
	Missing	0	0	0
HDL cholesterol (mmol/L)				
	Mean (SD)	1.06 (0.32)	1.09 (0.40)	1.07 (0.36)
	Median (IQR)	1.00 (0.88-1.30)	1.10 (0.80-1.40)	1.00 (0.88-1.30)
	Range	0.50-1.90	0.10-1.90	0.10-1.90
	Missing	0	0	0
LDL cholesterol (mmol/L)				
	Mean (SD)	1.47 (0.54)	1.25 (0.55)	1.37 (0.55)
	Median (IQR)	1.36 (1.10-1.90)	1.20 (0.80-1.50)	1.30 (0.90-1.70)
	Range	0.60-2.50	0.50-2.66	0.50-2.66
	Missing	1	0	1
Total cholesterol (mmol/L)				
	Mean (SD)	2.80 (0.67)	2.75 (0.66)	2.78 (0.66)
	Median (IQR)	2.60 (2.30-3.50)	2.60 (2.30-3.00)	2.60 (2.30-3.12)
	Range	2.00-4.20	2.00-4.90	2.00-4.90
	Missing	0	0	0
Triglycerides (mmol/L)				
	Mean (SD)	1.17 (0.77)	1.00 (0.53)	1.09 (0.67)
	Median (IQR)	0.90 (0.70-1.45)	0.90 (0.68-1.20)	0.90 (0.70-1.40)
	Range	0.40-4.00	0.14-2.10	0.14-4.00
	Missing	0	0	0
Creatine kinase (iu/L)				
	Mean (SD)	67.15 (33.13)	83.83 (55.31)	74.82 (45.02)
	Median (IQR)	63.00 (39.00-80.00)	68.00 (57.00-80.00)	67.00 (46.00-80.00)
	Range	30.00-168.00	36.00-256.00	30.00-256.00
	Missing	0	0	0
C Reactive Protein (mg/L)				
	Mean (SD)	10.46 (14.29)	7.48 (8.41)	9.09 (11.93)
	Median (IQR)	5.00 (4.80-7.00)	5.00 (3.00-7.00)	5.00 (4.00-7.00)
	Range	1.00-67.00	1.00-32.00	1.00-67.00
	Missing	0	0	0
Spirometry				
FEV in 1 second				
	Mean (SD)	2.10 (1.30)	1.86 (0.91)	2.00 (1.14)
	Median (IQR)	1.80 (1.43-2.68)	1.63 (1.18-2.34)	1.70 (1.37-2.48)
	Range	0.78-7.46	0.54-4.06	0.54-7.46
	Missing	0	2	2
FEV in 1 second (% predicted)				
	Mean (SD)	74.05 (17.57)	73.98 (19.59)	74.02 (18.28)
	Median (IQR)	76.00 (63.00-88.00)	75.00 (65.00-86.80)	75.50 (64.00-87.40)
	Range	27.00-104.00	35.00-105.00	27.00-105.00
	Missing	0	2	2

Baseline Characteristic	Control N=27	Rosuvastatin N=23	Total N=50
Urine Results			
KIM-1 (normalised to urinary creatinine (ng/mgCr))			
Mean (SD)	1.94 (2.45)	0.67 (0.45)	1.36 (1.93)
Median (IQR)	0.85 (0.48-2.45)	0.55 (0.31-1.01)	0.70 (0.41-1.44)
Range	0.18-9.50	0.10-1.54	0.10-9.50
Missing	3	3	6[1]
NGAL (normalised to urinary creatinine (ng/mgCr))			
Mean (SD)	61.08 (89.55)	22.46 (22.99)	43.52 (70.01)
Median (IQR)	30.71 (9.50-68.18)	15.21 (8.31-28.89)	18.61 (9.11-39.68)
Range	3.46-398.45	3.64-104.52	3.46-398.45
Missing	3	3	6[1]

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis - Baseline.sas*

6.2 Study population

Table 6.2: Data sets analysed

Population	Control	Rosuvastatin	Total
Screened	-	-	267
Randomised	27	23	50
Intention-to-treat	27	23	50 (100.00%)
Primary Outcome	24	20	44 (88.00%)
Safety	27	21	48 (96.00%)

Table 6.3: Protocol deviations

Protocol deviations: n (%)	Control (N=27)	Rosuvastatin (N=23)	Total (N=50)
Any protocol deviation	27 (100%)	23 (100%)	50 (100%)
At least one major:	**22 (81%)**	**19 (83%)**	**41 (82%)**
PD1 - Participant does not take their scheduled dose of rosuvastatin	N/A	4 (17%)	4 (8%)
PD2 - Participant receives an additional dose of rosuvastatin	N/A	1 (4%)	1 (2%)
PD3 - Premature discontinuation from tobramycin	4 (15%)	5 (22%)	9 (18%)
PD4 - Premature discontinuation from rosuvastatin	N/A	5 (22%)	5 (10%)
PD5 - Missing assessments visits and therefore missing primary outcome data[1]	18 (67%)	9 (39%)	27 (54%)
PD6 - Attendance at any of the treatment visits (T+1, T+8, T+13) outside allowed visit scheduled as documented in protocol	16 (59%)	11 (48%)	27 (54%)
PD7 - Blood samples not taken (local labs)[2]	6 (22%)	4 (17%)	10 (20%)
At least one minor:	**27 (100%)**	**23 (100%)**	**50 (100%)**
PD8 - Participant continues to take rosuvastatin following discontinuation of tobramycin	0 (0%)	2 (9%)	2 (4%)
PD9 - Participant does not take their scheduled dose of tobramycin	7 (26%)	5 (22%)	12 (24%)
PD10 - Sputum samples not taken	27 (100%)	23 (100%)	50 (100%)
PD11 - Blood samples not taken (central analysis)[3]	18 (67%)	20 (88%)	38 (76%)
PD12 - Attendance at 4 week visit outside allowed visit scheduled as documented in protocol	13 (48%)	8 (35%)	21 (42%)
PD13 - Participants failed to attend 4 week visit	2 (7%)	3 (13%)	5 (10%)

[1]Urine samples were taken daily during tobramycin treatment – if at least one sample is missing the participant has been included in this deviation.
[2]Blood samples for the local labs were taken at baseline, T+1, T+8 and T+13/final day of treatment – if at least one sample is missing the participant has been included in this deviation.
[3]Blood samples for central analysis were taken at baseline, T+1, T+8, T+13/final day of treatment and at 4 weeks following treatment cessation – if at least one sample is missing the participant has been included in this deviation.

Table 6.4: Protocol deviations split by site

Site	Major Deviation[1]							Minor Deviation[1]					
	PD1	PD2	PD3	PD4	PD5	PD6	PD7	PD8	PD9	PD10	PD11	PD12	PD13
	4	1	9	5	27	27	10	2	12	50	38	21	5
00002 - Royal Devon and Exeter	0	0	0	0	3	2	0	0	1	3	2	0	0
00031 - Leicester Royal Infirmary	0	0	2	2	2	3	0	0	2	5	5	4	0
00083 - Countess of Chester Hospital	0	0	0	0	0	0	0	0	0	1	1	0	0
00116 - Bristol Royal Hospital for Children	1	0	1	1	1	3	0	0	2	5	2	2	0
00133 – Birmingham Children's Hospital	0	0	0	0	0	0	0	0	0	2	0	1	0
00161 - King's College Hospital	1	0	0	0	2	1	0	0	1	3	3	1	1
00182 - University Hospital North Midlands	0	0	0	0	3	6	4	0	1	7	6	2	1
00243 - Alder Hey Children's Hospital	1	0	0	0	2	0	2	0	1	2	2	0	0
00248 - Sheffield Children's Hospital	0	0	0	0	3	3	2	0	0	5	2	3	0
00249 - Great Ormond Street Hospital	0	1	5	2	4	3	1	0	1	7	6	4	1
09888 - Royal Alexandra Children's Hospital	0	0	0	0	1	0	0	0	0	1	1	0	0
14570 - Nottingham Children's Hospital	1	0	1	0	6	6	1	2	3	9	8	4	2

[1]See previous table for protocol deviation definitions.

Table 6.5: Overall protocol deviations by site

Site	Number (%) of participants with at least one protocol deviation	Number (%) of participants with at least one major protocol deviation	Number (%) of participants with at least one minor protocol deviation
00002 - Royal Devon and Exeter	3 (100%)	3 (100%)	3 (100%)
00031 - Leicester Royal Infirmary	5 (100%)	3 (60%)	5 (100%)
00083 - Countess of Chester Hospital	1 (100%)	0 (0%)	1 (100%)
00116 - Bristol Royal Hospital for Children	5 (100%)	3 (60%)	5 (100%)
00133 – Birmingham Children's Hospital	2 (100%)	0 (0%)	2 (100%)
00161 - King's College Hospital	3 (100%)	2 (67%)	3 (100%)
00182 - University Hospital North Midlands	7 (100%)	6 (86%)	7 (100%)
00243 - Alder Hey Children's Hospital	2 (100%)	2 (100%)	2 (100%)
00248 - Sheffield Children's Hospital	5 (100%)	3 (60%)	5 (100%)
00249 - Great Ormond Street Hospital	7 (100%)	5 (71%)	7 (100%)
09888 - Royal Alexandra Children's Hospital	1 (100%)	1 (100%)	1 (100%)
14570 - Nottingham Children's Hospital	9 (100%)	6 (67%)	9 (100%)

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Protocol Deviations.sas*

6.3 Completeness of follow up

6.3.1 Withdrawal from follow-up

Table 6.6: Withdrawal from follow-up

Participant	Site	Treatment group	Date of randomisation	Date of withdrawal	Reason for withdrawal
00161005	King's College Hospital	Rosuvastatin	14-Sep-15	14-Sep-15	Withdrawal of consent for follow-up at baseline prior to treatment start.
00249012	Great Ormond Street Hospital	Rosuvastatin	16-Nov-15	16-Nov-15	Participant discharged prior to treatment start and not willing to continue in the study as an outpatient.
00182046	University Hospital North Midlands	Control	01-Nov-16	28-Nov-16	Clinician decision to withdraw due to loss of contact with participant.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Withdrawals.sas*

6.4 Completeness of Primary Outcome Data

Table 6.7: Line listing of samples collected

Participant	Expected number samples [a]	Actual number of samples (% of [a])	Number of samples missing (% of [a])
00002032	12	11 (91.67%)	1 (8.33%)
00002034	13	12 (92.31%)	1 (7.69%)
00002043	14	6 (42.86%)	8 (57.14%)
00031013	11	11 (100%)	0 (0.00%)
00031018	14	14 (100%)	0 (0.00%)
00031026	15	13 (86.67%)	2 (13.33%)
00031027	14	13 (92.86%)	1 (7.14%)
00031037	8	8 (100%)	0 (0.00%)
00083041	14	14 (100%)	0 (0.00%)
00116007	15	15 (100%)	0 (0.00%)
00116008	14	14 (100%)	0 (0.00%)
00116025	15	15 (100%)	0 (0.00%)
00116029	12	12 (100%)	0 (0.00%)
00116031	15	14 (93.33%)	1 (6.67%)
00133045	14	14 (100%)	0 (0.00%)
00133048	14	14 (100%)	0 (0.00%)
00161002	14	13 (92.86%)	1 (7.14%)
00161017	14	12 (85.71%)	2 (14.29%)
00182016	14	14 (100%)	0 (0.00%)
00182019	14	11 (78.57%)	3 (21.43%)
00182021	14	12 (85.71%)	2 (14.29%)
00182038	14	14 (100%)	0 (0.00%)
00182042	14	14 (100%)	0 (0.00%)
00182044	14	13 (92.86%)	1 (7.14%)
00182046	14	14 (100%)	0 (0.00%)
00243006	15	8 (53.33%)	7 (46.67%)
00243011	15	14 (93.33%)	1 (6.67%)
00248001	14	12 (85.71%)	2 (14.29%)
00248010	15	15 (100%)	0 (0.00%)
00248022	13	14 (107.69%)	0 (0.00%)
00248028	14	9 (64.29%)	5 (35.71%)
00248047	14	13 (92.86%)	1 (7.14%)
00249001	12	12 (100%)	0 (0.00%)
00249004	14	15 (107.14%)	0 (0.00%)
00249014	13	12 (92.31%)	1 (7.69%)
00249015	13	12 (92.31%)	1 (7.69%)
00249020	13	12 (92.31%)	1 (7.69%)
00249049	13	10 (76.92%)	3 (23.08%)
09888024	14	13 (92.86%)	1 (7.14%)
14570003	14	14 (100%)	0 (0.00%)
14570023	13	9 (69.23%)	4 (30.77%)
14570030	9	6 (66.67%)	3 (33.33%)
14570033	14	6 (42.86%)	8 (57.14%)
14570035	15	15 (100%)	0 (0.00%)
14570036	14	14 (100%)	0 (0.00%)
14570039	13	12 (92.31%)	1 (7.69%)
14570040	13	12 (92.31%)	1 (7.69%)
14570901	15	10 (66.67%)	5 (33.33%)
Total	**652**	**586 (89.88%)**	**68 (10.12%)**

Note: Rows highlighted in grey indicate participants who did not have a valid baseline sample (i.e. baseline sample was taking after commencement of treatment).

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Missing Data.sas*

Table 6.8: Missing primary outcome data by site

Site	Number of expected samples	Number of samples according to the sample log/sample information sheets (% of number expected) [a]	[b] Number of urine samples transferred from local site to central lab (% of [a])	[c] Number of urine samples received by central lab (% of [b])	[d] Number of urine samples viable for analysis (% of [c])	Number of urine samples included within primary outcome analysis (% of [d])
00002 - Royal Devon and Exeter	39	32 (82.05%)	32 (100%)	32 (100%)	32 (100%)	29 (90.63%)
00031 - Leicester Royal Infirmary	62	61 (98.39%)	61 (100%)	61 (100%)	61 (100%)	51 (83.61%)
00083 - Countess of Chester Hospital	14	14 (100%)	14 (100%)	14 (100%)	14 (100%)	14 (100%)
00116 - Bristol Royal Hospital for Children	71	71 (100%)	71 (100%)	71 (100%)	71 (100%)	70 (98.59%)
00133 – Birmingham Children's Hospital	28	28 (100%)	28 (100%)	28 (100%)	28 (100%)	28 (100%)
00161 - King's College Hospital	28	28 (100%)	28 (100%)	28 (100%)	27 (96.43%)	25 (92.59%)
00182 - University Hospital North Midlands	98	93 (94.90%)	93 (100%)	93 (100%)	93 (100%)	68 (73.12%)
00243 - Alder Hey Children's Hospital	30	22 (73.33%)	22 (100%)	22 (100%)	22 (100%)	22 (100%)
00248 - Sheffield Children's Hospital	70	64 (91.43%)	64 (100%)	64 (100%)	64 (100%)	63 (98.44%)
00249 - Great Ormond Street Hospital	78	76 (97.44%)	76 (100%)	76 (100%)	75 (98.68%)	73 (97.33%)
09888 - Royal Alexandra Children's Hospital	14	14 (100%)	14 (100%)	14 (100%)	13 (92.86%)	13 (100%)
14570 - Nottingham Children's Hospital	120	103 (85.83%)	103 (100%)	103 (100%)	101 (98.06%)	84 (83.17%)
Total	**652**	**606 (92.94%)**	**606 (100%)**	**606 (100%)**	**601 (99.17%)[1]**	**540 (89.85%)[2]**

[1]One sample was destroyed and 4 samples were lost.
[2]46 samples were excluded due to 6 participants not having a valid baseline sample; 8 samples were excluded due to being repeated baseline samples (i.e. prior to treatment start); 7 samples were excluded due to having a missing date.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Missing Data.sas*

Table 6.9: Line listings of participants with missing baseline urine samples

Participant	Treatment Group	Reason(s)
00161005	Rosuvastatin	Participant withdrew at baseline before commencing treatment
00249012	Rosuvastatin	Participant withdrew at baseline before commencing treatment
00182019	Control	Sample was taken after commencing treatment
14570036	Control	Sample was taken after commencing treatment
00031037	Rosuvastatin	Sample was taken after commencing treatment
00182044	Control	Sample was taken after commencing treatment

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Missing Data.sas*

6.5 Compliance

Table 6.10: Returned diaries

Site	Control		Rosuvastatin		Overall	
	Number of diary entries expected	Actual number of diary entries (% of expected)	Number of diary entries expected	Actual number of diary entries (% of expected)	Number of diary entries expected	Actual number of diary entries (% of expected)
00002 - Royal Devon and Exeter[1]	28	13 (46.43%)	12	12 (100%)	40	25 (62.50%)
00031 - Leicester Royal Infirmary	29	29 (100%)	35	34 (97.14%)	64	63 (98.44%)
00083 - Countess of Chester Hospital	0	0 (100%)	14	14 (100%)	14	14 (100%)
00116 - Bristol Royal Hospital for Children	45	41 (91.11%)	28	28 (100%)	73	69 (94.52%)
00133 – Birmingham Children's Hospital	14	14 (100%)	14	14 (100%)	28	28 (100%)
00161 - King's College Hospital	14	14 (100%)	14	3 (21.43%)	28	17 (60.71%)
00182 - University Hospital North Midlands	57	55 (96.49%)	42	42 (100%)	99	97 (97.98%)
00243 - Alder Hey Children's Hospital	15	15 (100%)	15	15 (100%)	30	30 (100%)
00248 - Sheffield Children's Hospital	43	42 (97.67%)	28	28 (100%)	71	70 (98.59%)
00249 - Great Ormond Street Hospital[1]	55	55 (100%)	25	12 (48.00%)	80	67 (83.75%)
09888 - Royal Alexandra Children's Hospital	14	14 (100%)	0	0 (100%)	14	14 (100%)
14570 - Nottingham Children's Hospital[1]	66	49 (74.24%)	58	58 (100%)	124	107 (86.29%)
Total	**380**	**341 (89.74%)**	**285**	**260 (91.23%)**	**665**	**601 (90.38%)**

[1]Site had a participant who did not return a treatment diary.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Compliance.sas*

Table 6.11: Premature treatment discontinuation

Site	Participant	Treatment group	Date of randomisation	Date of discontinuation of tobramycin	Date of discontinuation of rosuvastatin	Days on treatment	Decision made by	Reason for discontinuation
Leicester Royal Infirmary	00031013	Rosuvastatin	23-Nov-15	04-Dec-15	04-Dec-15	11	Clinician	Change to the patient's condition that justifies discontinuation of treatment in the clinician's opinion: No longer clinically indicated.
	00031037	Rosuvastatin	16-Aug-16	23-Aug-16	23-Aug-16	7	Clinician	Line failure
Bristol Royal Hospital for Children	00116029	Rosuvastatin	27-Jun-16	09-Jul-16	09-Jul-16	12	Participant / Parent / Guardian	Change to the patient's condition that justifies discontinuation of treatment in the clinician's opinion
Great Ormond Street Hospital	00249001	Rosuvastatin	29-Jun-15	10-Jul-15	10-Jul-15	11	Participant / Parent / Guardian / Clinician	Change to the patient's condition that justifies discontinuation of treatment in the clinician's opinion
	00249014	Control	23-Nov-15	05-Dec-15	N/A	12	Unobtainable	No reason given.
	00249015	Rosuvastatin	25-Nov-15	07-Dec-15	07-Dec-15	12	Clinician	Change to the patient's condition that justifies discontinuation of treatment in the clinician's opinion
	00249020	Control	10-Mar-16	23-Mar-16	N/A	13	Clinician	Clinical decision to stop on day 13
	00249049	Control	23-Jan-17	04-Feb-17	N/A	12	Clinician	Change to the patient's condition that justifies discontinuation of treatment in the clinician's opinion
Nottingham Children's Hospital	14570030	Control	29-Jun-16	07-Jul-16	N/A	8	Clinician	Clinical decision to cease

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Premature Discont.sas*

Table 6.12: Tobramycin compliance

Randomisation number	Expected number of days tobramycin to be taken[A]	Actual number of days tobramycin taken (% of expected)	Missed doses		
			Number of doses recorded as 'Not taken' in diary [A]	Number of doses not recorded in diary [B]	Total number of days missed tobramycin doses [A+B] (% of expected)
00002032	12	12 (100%)	0	0	0 (0%)
00002034	13	12 (92.31%)	1	0	1 (7.69%)
00002043	14	**No treatment diary**			
00031013	11	11 (100%)	0	0	0 (0%)
00031018	14	14 (100%)	0	0	0 (0%)
00031026	15	14 (93.33%)	1	0	1 (6.67%)
00031027	14	14 (100%)	0	0	0 (0%)
00031037	8	7 (87.50%)	1	0	1 (12.50%)
00083041	14	14 (100%)	0	0	0 (0%)
00116007	15	15 (100%)	0	0	0 (0%)
00116008	14	14 (100%)	0	0	0 (0%)
00116025	15	13 (86.67%)	0	2	2 (13.33%)
00116029	12	12 (100%)	0	0	0 (0%)
00116031	15	12 (80.00%)	2	1	3 (20.00%)
00133045	14	14 (100%)	0	0	0 (0%)
00133048	14	14 (100%)	0	0	0 (0%)
00161002	14	14 (100%)	0	0	0 (0%)
00161005	**Withdrawal at baseline**				
00161017	14	3 (21.43%)	0	11	11 (78.57%)
00182016	14	14 (100%)	0	0	0 (0%)
00182019	14	14 (100%)	0	0	0 (0%)
00182021	14	14 (100%)	0	0	0 (0%)
00182038	14	14 (100%)	0	0	0 (0%)
00182042	14	14 (100%)	0	0	0 (0%)
00182044	14	14 (100%)	0	0	0 (0%)
00182046	14	13 (92.86%)	0	1	1 (7.14%)
00243006	15	15 (100%)	0	0	0 (0%)
00243011	15	14 (93.33%)	1	0	1 (6.67%)
00248001	14	14 (100%)	0	0	0 (0%)
00248010	15	15 (100%)	0	0	0 (0%)
00248022	13	12 (92.31%)	0	1	1 (6.67%)
00248028	14	14 (100%)	0	0	0 (0%)
00248047	14	14 (100%)	0	0	0 (0%)
00249001	12	12 (100%)	0	0	0 (0%)
00249004	14	14 (100%)	0	0	0 (0%)
00249012	**Withdrawal at baseline**				
00249014	13	13 (100%)	0	0	0 (0%)
00249015	13	**No treatment diary**			
00249020	13	12 (92.31%)	1	0	1 (7.69%)
00249049	13	13 (100%)	0	0	0 (0%)
09888024	14	14 (100%)	0	0	0 (0%)
14570003	14	14 (100%)	0	0	0 (0%)
14570023	13	13 (100%)	0	0	0 (0%)
14570030	9	9 (100%)	0	0	0 (0%)
14570033	14	13 (92.86%)	1	0	1 (7.14%)
14570035	15	14 (93.33%)	1	0	1 (6.67%)
14570036	14	13 (92.86%)	1	0	1 (7.14%)
14570039	13	13 (100%)	0	0	0 (0%)
14570040	13	13 (100%)	0	0	0 (0%)
14570901	15	**No treatment diary**			
Total	**652**	**584 (89.57%)**	**10**	**16**	**26 (3.99%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Compliance.sas*

Table 6.13: Tobramycin compliance – Overall summary statistics by site

Site	N[1]	Expected number of days tobramycin to be taken[2]			Actual number of days tobramycin taken			Missing		
		Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
00002	2	12.50 (0.71)	12.50 (12.00, 13.00)	12.00, 13.00	12.00 (0.00)	12.00 (12.00, 12.00)	12.00, 12.00	0.50 (0.71)	0.50 (0.00, 1.00)	0.00, 1.00
00031	5	12.40 (2.88)	14.00 (11.00, 14.00)	8.00, 15.00	12.00 (3.08)	14.00 (11.00, 14.00)	7.00, 14.00	0.40 (0.55)	0.00 (0.00, 1.00)	0.00, 1.00
00083	1	14.00 (N/A)	14.00 (14.00, 14.00)	14.00, 14.00	14.00 (N/A)	14.00 (14.00, 14.00)	14.00, 14.00	0.00 (N/A)	0.00 (0.00, 0.00)	0.00, 0.00
00116	5	14.20 (1.30)	15.00 (14.00, 15.00)	12.00, 15.00	13.20 (1.30)	13.00 (12.00, 14.00)	12.00, 15.00	1.00 (1.41)	0.00 (0.00, 2.00)	0.00, 3.00
00133	2	14.00 (0.00)	14.00 (14.00, 14.00)	14.00, 14.00	14.00 (0.00)	14.00 (14.00, 14.00)	14.00, 14.00	0.00 (0.00)	0.00 (0.00, 0.00)	0.00, 0.00
00161	2	14.00 (0.00)	14.00 (14.00, 14.00)	14.00, 14.00	8.50 (7.78)	8.50 (3.00, 14.00)	3.00, 14.00	5.50 (7.78)	5.50 (0.00, 11.00)	0.00, 11.00
00182	7	14.00 (0.00)	14.00 (14.00, 14.00)	14.00, 14.00	13.86 (0.38)	14.00 (14.00, 14.00)	13.00, 14.00	0.14 (0.38)	0.00 (0.00, 0.00)	0.00, 1.00
00243	2	15.00 (0.00)	15.00 (15.00, 15.00)	15.00, 15.00	14.50 (0.71)	14.50 (14.00, 15.00)	14.00, 15.00	0.50 (0.71)	0.50 (0.00, 1.00)	0.00, 1.00
00248	5	14.00 (0.71)	14.00 (14.00, 14.00)	13.00, 15.00	13.80 (1.10)	14.00 (14.00, 14.00)	12.00, 15.00	0.20 (0.45)	0.00 (0.00, 0.00)	0.00, 1.00
00249	5	13.00 (0.71)	13.00 (13.00, 13.00)	12.00, 14.00	12.80 (0.84)	13.00 (12.00, 13.00)	12.00, 14.00	0.20 (0.45)	0.00 (0.00, 0.00)	0.00, 1.00
09888	1	14.00 (N/A)	14.00 (14.00, 14.00)	14.00, 14.00	14.00 (N/A)	14.00 (14.00, 14.00)	14.00, 14.00	0.00 (N/A)	0.00 (0.00, 0.00)	0.00, 0.00
14570	8	13.13 (1.81)	13.50 (13.00, 14.00)	9.00, 15.00	12.75 (1.58)	13.00 (13.00, 13.50)	9.00, 14.00	0.38 (0.52)	0.00 (0.00, 1.00)	0.00, 1.00
Total	**45**	**13.56 (1.42)**	**14.00 (13.00, 14.00)**	**8.00, 15.00**	**12.98 (2.12)**	**14.00 (13.00, 14.00)**	**3.00, 15.00**	**0.58 (1.71)**	**0.00 (0.00, 1.00)**	**0.00, 11.00**

[1] Participants only included if they returned a treatment diary and did not withdraw at baseline.
[2] Number of days from date of first dose to end of treatment date.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Compliance.sas*

Table 6.14: Tobramycin compliance – Control group summary statistics by site

Site	N[1]	Expected number of days tobramycin to be taken[2]			Actual number of days tobramycin taken			Missing		
		Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
00002	1	13.00 (NA)	13.00 (13.00, 13.00)	(13.00, 13.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	1.00 (NA)	1.00 (1.00, 1.00)	(1.00, 1.00)
00031	2	14.50 (0.71)	14.50 (14.00, 15.00)	(14.00, 15.00)	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.50 (0.71)	0.50 (0.00, 1.00)	(0.00, 1.00)
00116	3	14.67 (0.58)	15.00 (14.00, 15.00)	(14.00, 15.00)	13.00 (1.00)	13.00 (12.00, 14.00)	(12.00, 14.00)	1.67 (1.53)	2.00 (0.00, 3.00)	(0.00, 3.00)
00133	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00161	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00182	4	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	13.75 (0.50)	14.00 (13.50, 14.00)	(13.00, 14.00)	0.25 (0.50)	0.00 (0.00, 0.50)	(0.00, 1.00)
00243	1	15.00 (NA)	15.00 (15.00, 15.00)	(15.00, 15.00)	15.00 (NA)	15.00 (15.00, 15.00)	(15.00, 15.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00248	3	14.00 (1.00)	14.00 (13.00, 15.00)	(13.00, 15.00)	13.67 (1.53)	14.00 (12.00, 15.00)	(12.00, 15.00)	0.33 (0.58)	0.00 (0.00, 1.00)	(0.00, 1.00)
00249	4	13.25 (0.50)	13.00 (13.00, 13.50)	(13.00, 14.00)	13.00 (0.82)	13.00 (12.50, 13.50)	(12.00, 14.00)	0.25 (0.50)	0.00 (0.00, 0.50)	(0.00, 1.00)
09888	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
14570	4	12.25 (2.22)	13.00 (11.00, 13.50)	(9.00, 14.00)	12.00 (2.00)	13.00 (11.00, 13.00)	(9.00, 13.00)	0.25 (0.50)	0.00 (0.00, 0.50)	(0.00, 1.00)
Total	**25**	**13.72 (1.21)**	**14.00 (13.00, 14.00)**	**(9.00, 15.00)**	**13.28 (1.24)**	**14.00 (13.00, 14.00)**	**(9.00, 15.00)**	**0.44 (0.77)**	**0.00 (0.00, 1.00)**	**(0.00, 3.00)**

[1] Participants only included if they returned a treatment diary and did not withdraw at baseline.
[2] Number of days from date of first dose to end of treatment date.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs \PROteKT Final Analysis – Compliance split by treatment.sas*

Table 6.15: Tobramycin compliance – Rosuvastatin group summary statistics by site

Site	N[1]	Expected number of days tobramycin to be taken[2]			Actual number of days tobramycin taken			Missing		
		Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
00002	1	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00031	3	11.00 (3.00)	11.00 (8.00, 14.00)	(8.00, 14.00)	10.67 (3.51)	11.00 (7.00, 14.00)	(7.00, 14.00)	0.33 (0.58)	0.00 (0.00, 1.00)	(0.00, 1.00)
00083	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00116	2	13.50 (2.12)	13.50 (12.00, 15.00)	(12.00, 15.00)	13.50 (2.12)	13.50 (12.00, 15.00)	(12.00, 15.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00133	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00161	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	3.00 (NA)	3.00 (3.00, 3.00)	(3.00, 3.00)	11.00 (NA)	11.00 (11.00, 11.00)	(11.00, 11.00)
00182	3	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00243	1	15.00 (NA)	15.00 (15.00, 15.00)	(15.00, 15.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	1.00 (NA)	1.00 (1.00, 1.00)	(1.00, 1.00)
00248	2	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00249	1	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
14570	4	14.00 (0.82)	14.00 (13.50, 14.50)	(13.00, 15.00)	13.50 (0.58)	13.50 (13.00, 14.00)	(13.00, 14.00)	0.50 (0.58)	0.50 (0.00, 1.00)	(0.00, 1.00)
Total	**20**	**13.35 (1.66)**	**14.00 (12.50, 14.00)**	**(8.00, 15.00)**	**12.60 (2.85)**	**14.00 (12.00, 14.00)**	**(3.00, 15.00)**	**0.75 (2.45)**	**0.00 (0.00, 0.50)**	**(0.00, 11.00)**

[1] Participants only included if they returned a treatment diary and did not withdraw at baseline.
[2] Number of days from date of first dose to end of treatment date.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs \PROteKT Final Analysis – Compliance split by treatment.sas*

Table 6.16: Rosuvastatin compliance line listing

Randomisation number	Expected number of days rosuvastatin to be taken[A]	Actual number of days rosuvastatin taken (% of expected)	Missed doses		
			Number of doses recorded as 'Not taken' in diary [A]	Number of doses not recorded in diary [B]	Total number of days missed rosuvastatin doses [A+B] (% of expected)
00002032	12	12 (100%)	0	0	0 (0%)
00031013	11	11 (100%)	0	0	0 (0%)
00031027	14	14 (100%)	0	0	0 (0%)
00031037	8	8 (100%)	0	0	0 (0%)
00083041	14	14 (100%)	0	0	0 (0%)
00116007	15	14 (93.33%)	1	0	1 (6.67%)
00116029	12	12 (100%)	0	0	0 (0%)
00133045	14	14 (100%)	0	0	0 (0%)
00161017	14	3 (21.43%)	0	11	11 (78.57%)
00182016	14	14 (100%)	0	0	0 (0%)
00182038	14	14 (100%)	0	0	0 (0%)
00182042	14	14 (100%)	0	0	0 (0%)
00243011	15	14 (93.33%)	1	0	1 (6.67%)
00248001	14	14 (100%)	0	0	0 (0%)
00248028	14	14 (100%)	0	0	0 (0%)
00249001	12	12 (100%)	0	0	0 (0%)
00249015	13	**No treatment diary**			
14570003	14	14 (100%)	0	0	0 (0%)
14570033	14	14 (100%)	0	0	0 (0%)
14570035	15	14 (93.33%)	1	0	1 (6.67%)
14570040	13	13 (100%)	0	0	0 (0%)
Total	**280**	**253 (90.36%)**	**3**	**11**	**24 (8.57%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs \PROteKT Final Analysis – Compliance - Rosuvastatin.sas*

Table 6.17: Rosuvastatin compliance – Summary statistics by site

Site	N[1]	Expected number of days rosuvastatin to be taken[2]			Actual number of days rosuvastatin taken			Missing		
		Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range
00002	1	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00031	3	11.00 (3.00)	11.00 (8.00, 14.00)	(8.00, 14.00)	11.00 (3.00)	11.00 (8.00, 14.00)	(8.00, 14.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00083	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00116	2	13.50 (2.12)	13.50 (12.00, 15.00)	(12.00, 15.00)	13.00 (1.41)	13.00 (12.00, 14.00)	(12.00, 14.00)	0.50 (0.71)	0.50 (0.00, 1.00)	(0.00, 1.00)
00133	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
00161	1	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	3.00 (NA)	3.00 (3.00, 3.00)	(3.00, 3.00)	11.00 (NA)	11.00 (11.00, 11.00)	(11.00, 11.00)
00182	3	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00243	1	15.00 (NA)	15.00 (15.00, 15.00)	(15.00, 15.00)	14.00 (NA)	14.00 (14.00, 14.00)	(14.00, 14.00)	1.00 (NA)	1.00 (1.00, 1.00)	(1.00, 1.00)
00248	2	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	14.00 (0.00)	14.00 (14.00, 14.00)	(14.00, 14.00)	0.00 (0.00)	0.00 (0.00, 0.00)	(0.00, 0.00)
00249	1	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
09888	4	14.00 (0.82)	14.00 (13.50, 14.50)	(13.00, 15.00)	13.75 (0.50)	14.00 (13.50, 14.00)	(13.00, 14.00)	0.25 (0.50)	0.00 (0.00, 0.50)	(0.00, 1.00)
14570	1	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	12.00 (NA)	12.00 (12.00, 12.00)	(12.00, 12.00)	0.00 (NA)	0.00 (0.00, 0.00)	(0.00, 0.00)
Total	**20**	13.35 (1.66)	14.00 (12.50, 14.00)	(8.00, 15.00)	12.65 (2.74)	14.00 (12.00, 14.00)	(3.00, 14.00)	0.70 (2.45)	0.00 (0.00, 0.00)	(0.00, 11.00)

[1] Participants only included if they returned a treatment diary and did not withdraw at baseline.
[2] Number of days from date of first dose to end of treatment date.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Closed\PROteKT Final Analysis – Compliance - Rosuvastatin.sas*

7. Safety data

- 12 adverse reactions were reported by 5 (25%) of the 21 patients randomised to rosuvastatin who received at least one dose of rosuvastatin.

7.1 Adverse reactions

Table 7.1: Adverse reactions

System Organ Class	Preferred term	Number of events	Number of participants *(% of those in safety analysis set n=21)*
Metabolism and nutrition disorders	Hypoglycaemia	2	1 (4.76%)
Investigations	Alanine aminotransferase increased	1	1 (4.76%)
	Aspartate aminotransferase increased	1	1 (4.76%)
	Blood cholesterol decreased	1	1 (4.76%)
	Blood creatine phosphokinase increased	1	1 (4.76%)
	Blood triglycerides decreased	1	1 (4.76%)
	Blood triglycerides increased	1	1 (4.76%)
Musculoskeletal and connective tissue disorders	Back pain	1	1 (4.76%)
Nervous system disorders	Headache	1	1 (4.76%)
	Paraesthesia	1	1 (4.76%)
	Paraesthesia oral	1	1 (4.76%)
	Total	**12**	**5 (23.81%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Safety.sas*

7.2 Adverse reactions by severity

Table 7.2: Adverse reactions by severity

System Organ Class	Preferred Term	Severity	Number of events	Number of participants *(% of those in safety analysis set n=21)*
Metabolism and nutrition disorders	Hypoglycaemia	Mild	2	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
Investigations	Alanine aminotransferase increased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Aspartate aminotransferase increased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Blood cholesterol decreased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Blood creatine phosphokinase increased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Blood triglycerides decreased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Blood triglycerides increased	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
Musculoskeletal and connective tissue disorders	Back pain	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
Nervous system disorders	Headache	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Paraesthesia	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
	Paraesthesia oral	Mild	1	1 (4.76%)
		Moderate	0	0 (0%)
		Severe	0	0 (0%)
		Missing	0	0 (0%)
Total		**Mild**	**12**	**5 (23.81%)**
		Moderate	**0**	**0 (0%)**
		Severe	**0**	**0 (0%)**
		Missing	**0**	**0 (0%)**

Note: Where patients have experienced more than one adverse reaction and more than one severity, they have been reported in the most severe category.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Safety.sas*

7.3 Adverse reactions by relatedness

Table 7.3: Adverse reactions by relatedness

System Organ Class	Preferred Term	Related to study drug	Number of events	Number of participants *(% of those in safety analysis set n=21)*
Metabolism and nutrition disorders	Hypoglycaemia	Possibly	2	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
Investigations	Alanine aminotransferase increased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Aspartate aminotransferase increased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Blood cholesterol decreased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Blood creatine phosphokinase increased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Blood triglycerides decreased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Blood triglycerides increased	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
Musculoskeletal and connective tissue disorders	Back pain	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
Nervous system disorders	Headache	Possibly	1	1 (4.76%)
		Probably	0	0 (0%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Paraesthesia	Possibly	0	0 (0%)
		Probably	1	1 (4.76%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
	Paraesthesia oral	Possibly	0	0 (0%)
		Probably	1	1 (4.76%)
		Almost certainly	0	0 (0%)
		Missing	0	0 (0%)
Total		**Possibly**	**10**	**4 (19.05%)**
		Probably	**2**	**1 (4.76%)**
		Almost certainly	**0**	**0 (0%)**
		Missing	**0**	**0 (0%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Safety.sas*

7.4 Serious Adverse Events

- From a total of 27 patients in the control group, 1 SAE was reported from 1 patient (3.70%) and from a total of 21 patients in the rosuvastatin group, 1 SAE was reported from 1 patient (4.76%).
- Of the SAEs reported, a total of 0 patients experienced SUSARs.

Table 7.4: Serious Adverse Events

Patient number	Treatment group	Preferred Term/System Organ Class	Description	Date	Serious Criteria	Severity	Expectedness	Relationship PI Assessment	Relationship CI Assessment	Outcome
00243011	Rosuvastatin	Blood test/ Investigations	On the final day (24/11/2015) blood tests for participant were done at 23:35. Results were: ▪ Potassium 7.0 (ref range 3.5 - 5.5) ▪ Sodium 151 (ref range 131-145). The participant was kept in hospital to repeat blood tests on 25/11/2015 at 11:04. Results were: ▪ Potassium 5.2 ▪ Sodium 142. Participant was discharged on 25/11/2015.	25-Nov-15	Prolonged existing hospitalisation	Mild	Not expected	Unrelated	Unrelated	Continued in trial and completed trial
00002043	Control	Infective pulmonary exacerbation of cystic fibrosis/ Infections and infestations	Recurrence of pulmonary exacerbation during follow-up required admission to initiate further course of IV antibiotics and support physiotherapy. Five days spent in hospital and a further 9 days of IV antibiotics at home.	28-Nov-16	Required Hospitalisation	Moderate	N/A	N/A	N/A	Continued in trial and completed trial

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Safety.sas*

8. Efficacy data

8.1 Primary Outcome

The primary outcome measure is the difference in mean fold-change in urinary KIM-1 from baseline to peak concentration during exposure to tobramycin between the rosuvastatin treated group and control group.

8.1.1 Primary outcome - Primary efficacy assessment

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak KIM-1 normalised to urinary creatinine between the treatment groups, controlling for the baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale; see Table 8.1 for the results.

Table 8.1: Primary Outcome – Primary efficacy assessment ANCOVA Results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	24	1.85	1.08	0.87, 1.35	0.48
Rosuvastatin	20	2.00			

*Adjusted for baseline normalised KIM-1.

Figure 8.1 - Figure 8.3 show the model diagnostics.

Figure 8.1: Histogram assessing normality of residuals

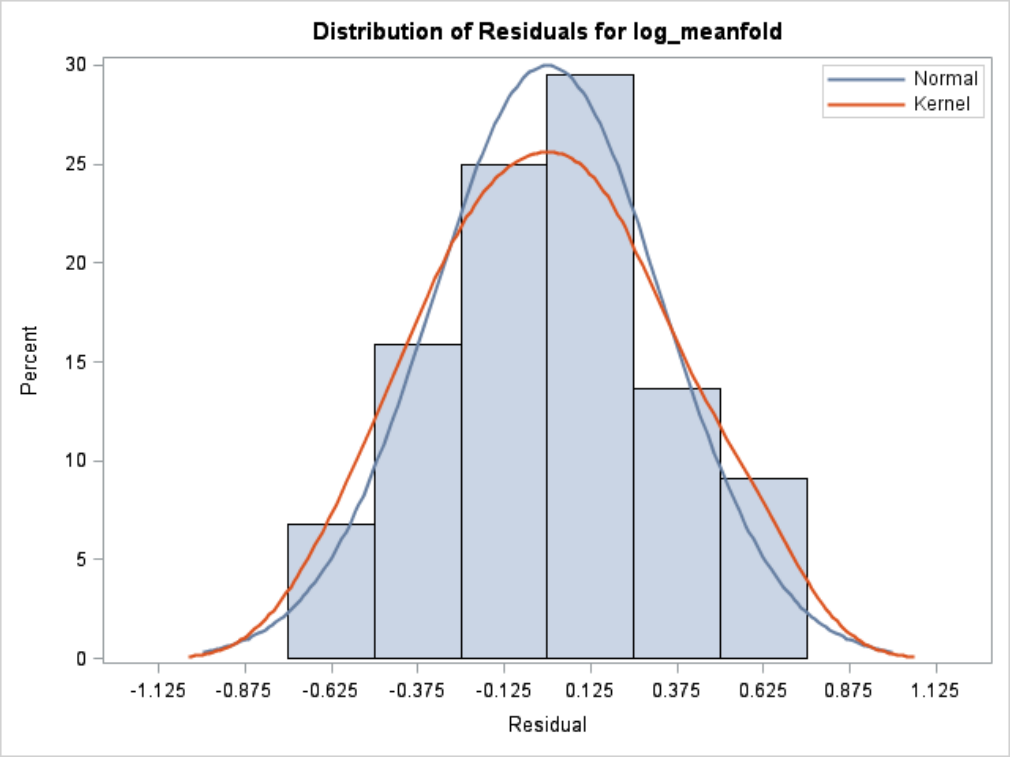


Figure 8.2: Q-Q plot assessing normality of residuals

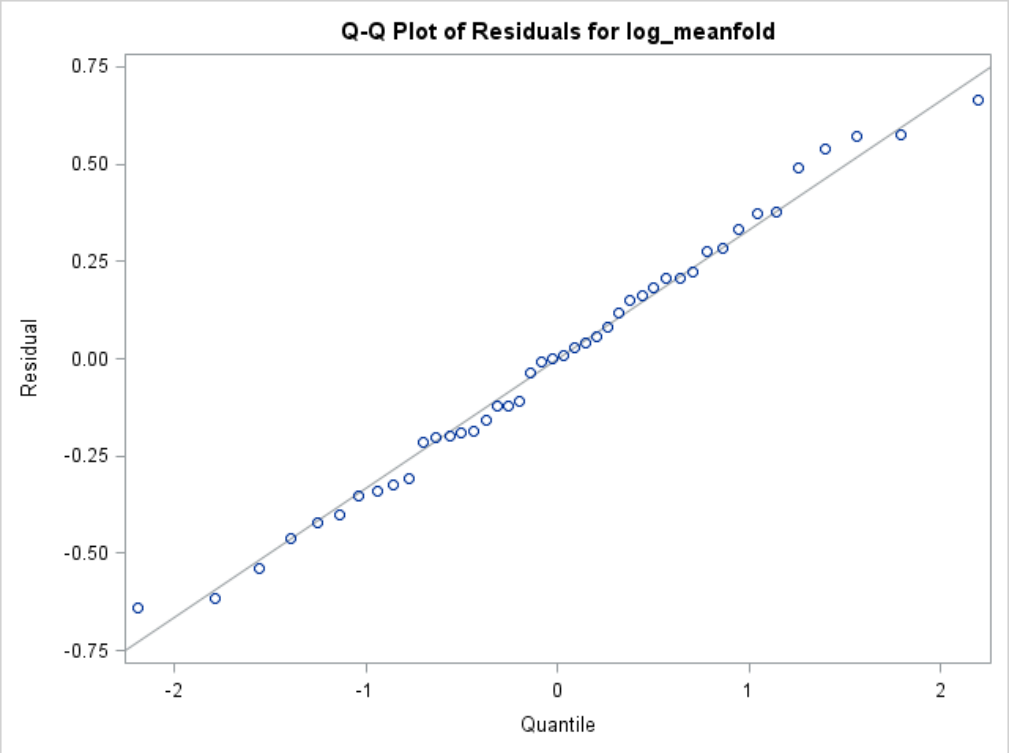
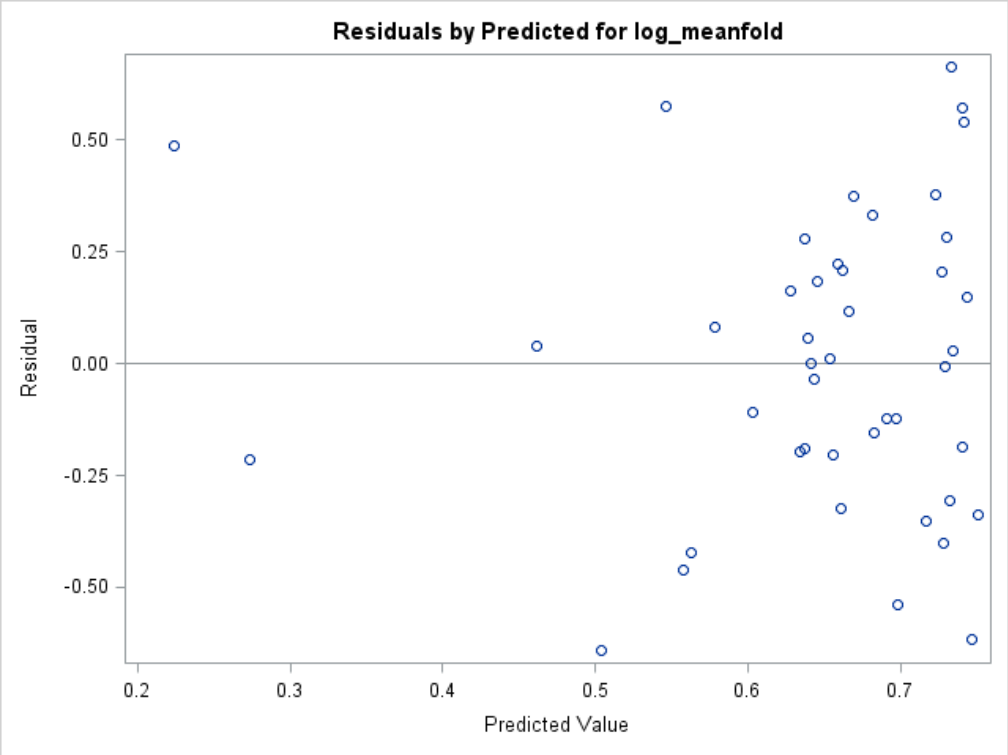


Figure 8.3: Scatter plot of residuals against fitted values assessing homoscedasticity



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs \PROteKT Final Analysis – Primary Outcome.sas*

8.1.2 Primary Outcome – Sensitivity Analysis 1

Sensitivity analysis 1 compared the difference in normalised KIM-1 from baseline to final day of treatment. For participants with a missing sample on day of last treatment, the result from the latest sample taken before the end of treatment was used. An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to last day of treatment between the treatment groups, controlling for baseline normalised KIM-1. The model estimates were exponentiated to be interpretable on the normal scale; see Table 8.2 for the results.

Table 8.2: Primary Outcome – Sensitivity Analysis 1: ANCOVA Results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	24	1.36	1.09	0.85, 1.39	0.48
Rosuvastatin	20	1.48			

*Adjusted for baseline normalised KIM-1.

Figure 8.4 - Figure 8.6 show the model diagnostics.

Figure 8.4: Histogram assessing normality of residuals for sensitivity analysis 1

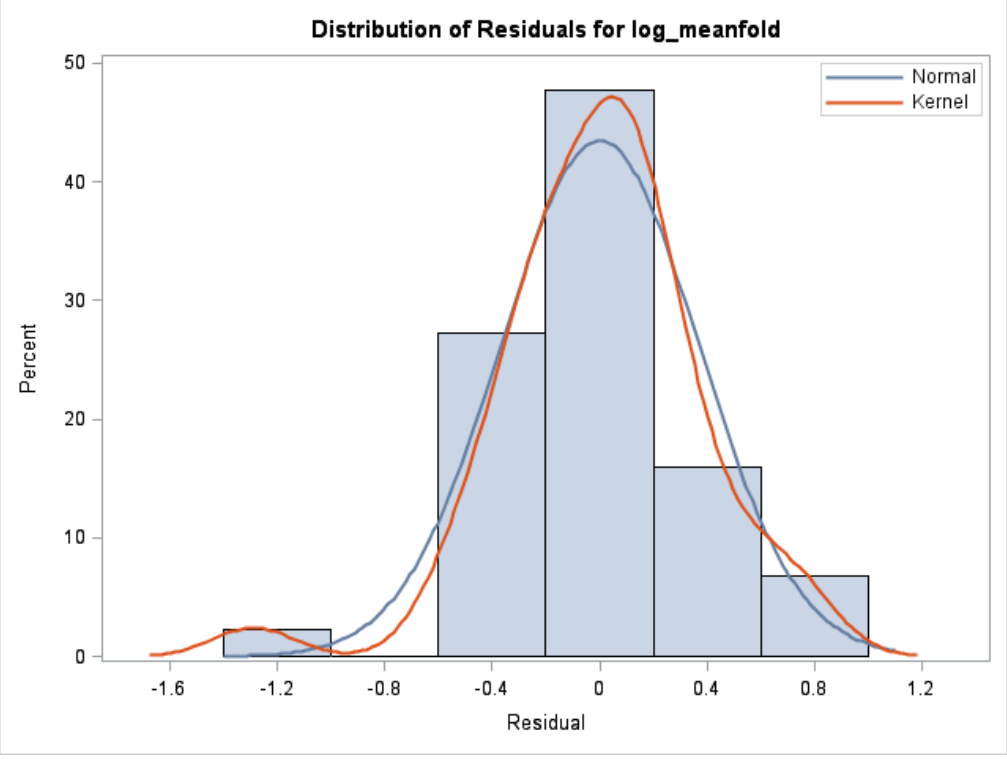


Figure 8.5: Q-Q plot assessing normality of residuals for sensitivity analysis 1

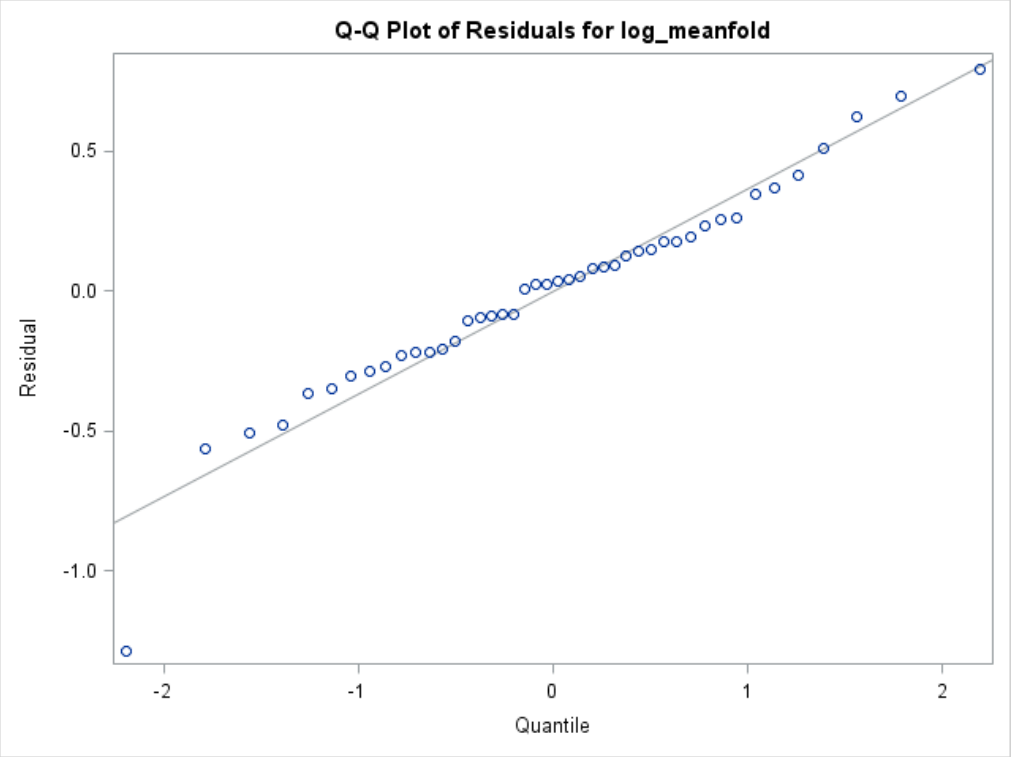
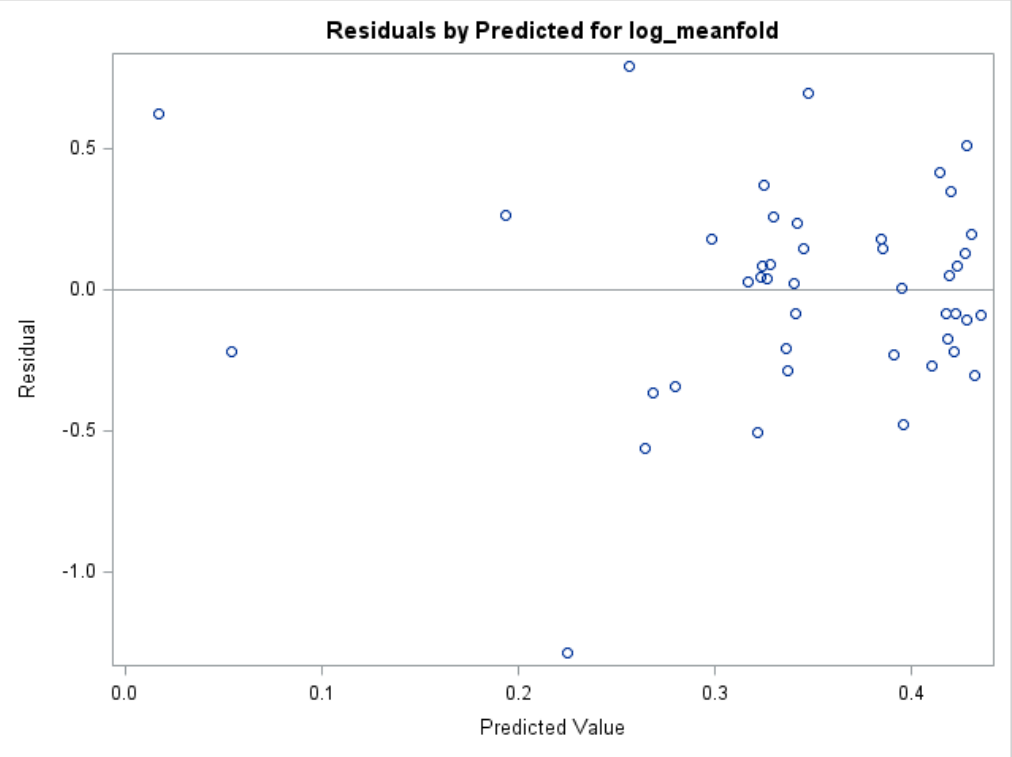


Figure 8.6: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 1



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Sensitivity analysis 1.sas*

8.1.3 Primary Outcome – Sensitivity Analysis 2

Sensitivity analysis 2 was a repeat of the analysis of the primary outcome, excluding those who returned less than 50% of urine samples. Two participants, each with 57% of samples missing, one in the control group and one in the rosuvastatin group, were excluded from this analysis. See Table 8.3 for the results.

Table 8.3: Primary Outcome – Sensitivity Analysis 2: ANCOVA Results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	23	1.89	1.07	0.68, 1.34	0.52
Rosuvastatin	19	2.03			

*Adjusted for baseline normalised KIM-1.

Figure 8.7 - Figure 8.9 show the model diagnostics.

Figure 8.7: Histogram assessing normality of residuals for sensitivity analysis 2

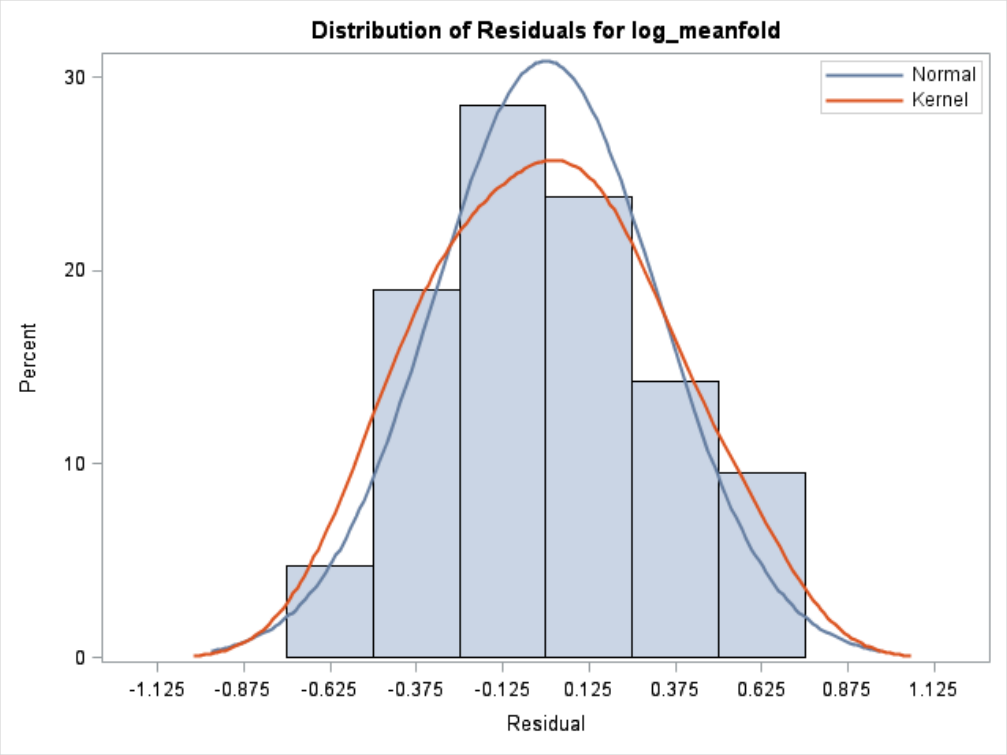


Figure 8.8: Q-Q plot assessing normality of residuals for sensitivity analysis 2

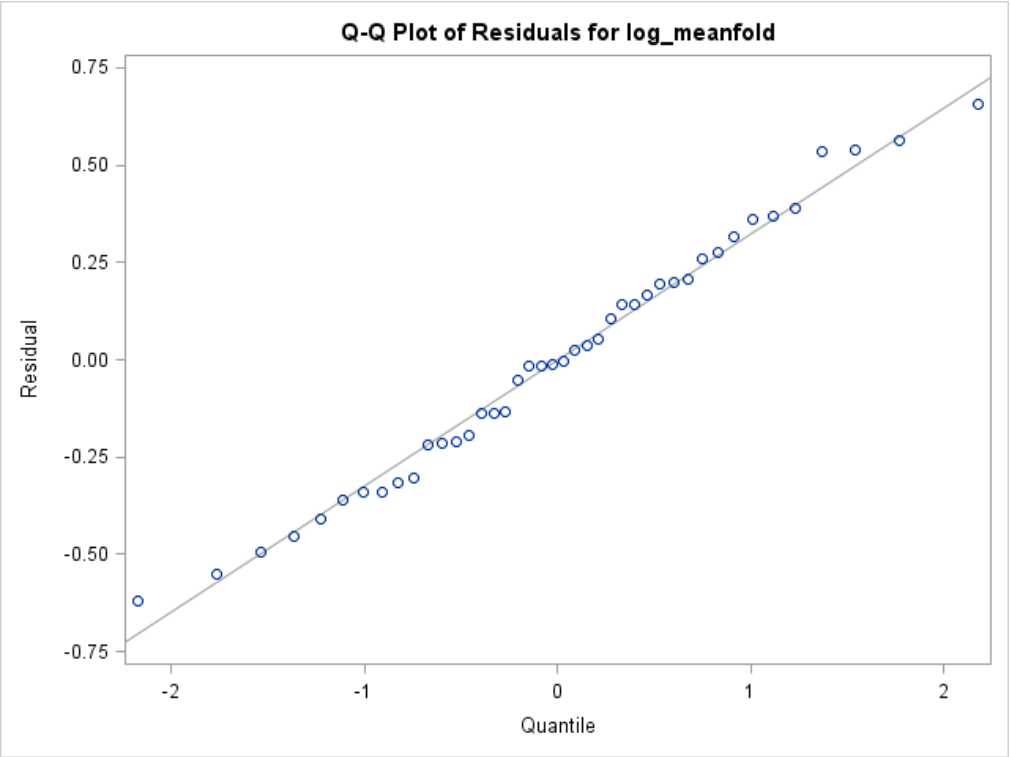
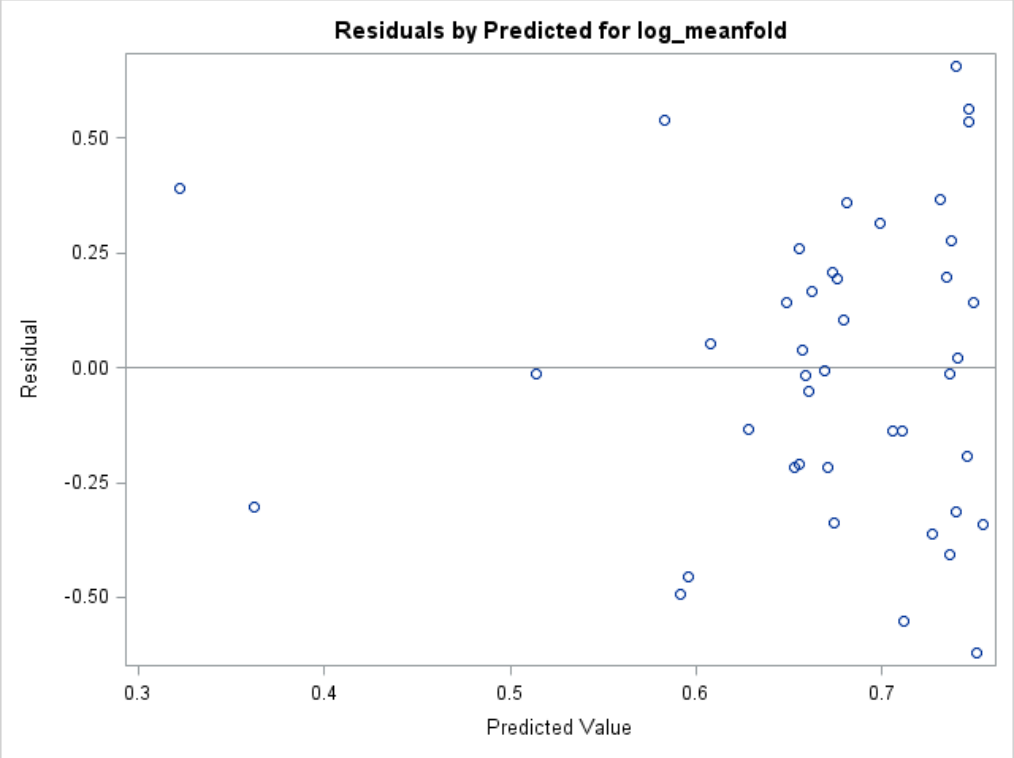


Figure 8.9: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 2



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Sensitivity analysis 2.sas*

8.1.4 Primary Outcome – Sensitivity Analysis 3

Sensitivity analysis 3 was a repeat of the analysis of the primary outcome, including participants who had a missing baseline sample by imputing their baseline result as the mean normalised KIM-1 value over all observed baseline KIM-1 values. See Table 8.4.

Table 8.4: Primary Outcome – Sensitivity Analysis 3: ANCOVA Results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	27	2.10	0.64	0.37, 1.10	0.10
Rosuvastatin	21	1.35			

*Adjusted for baseline normalised KIM-1.

Figure 8.10 - Figure 8.12 show the model diagnostics.

Figure 8.10: Histogram assessing normality of residuals for sensitivity analysis 3

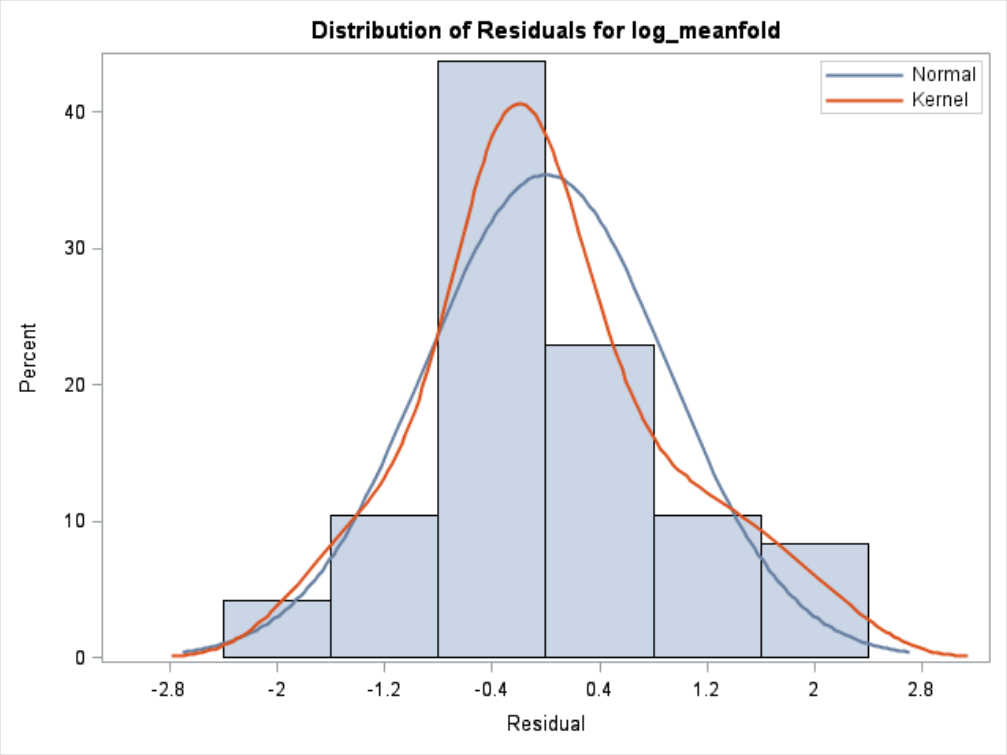


Figure 8.11: Q-Q plot assessing normality of residuals for sensitivity analysis 3

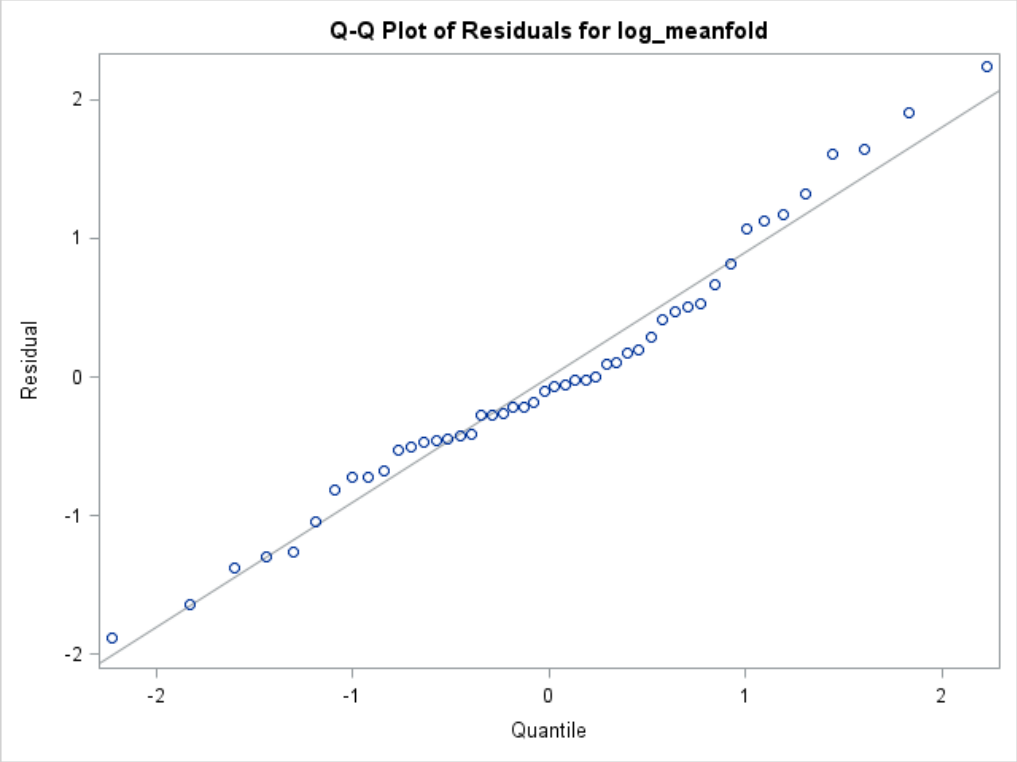
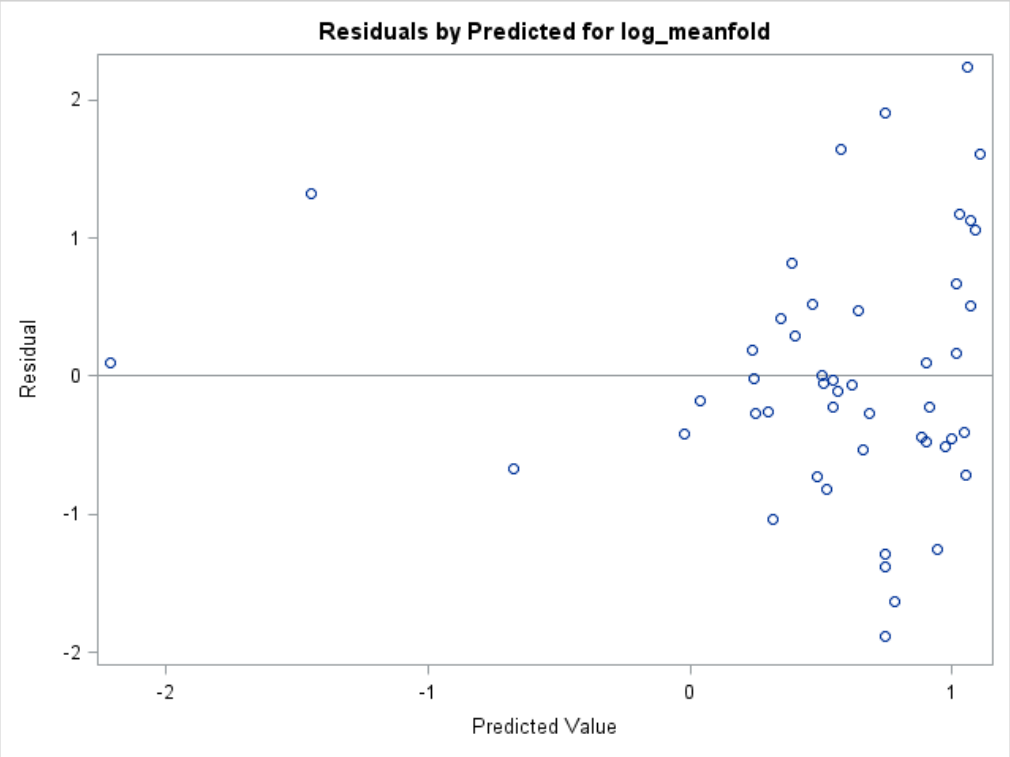


Figure 8.12: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 3



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Sensitivity analysis 3.sas*

8.1.5 Primary Outcome – Sensitivity Analysis 4

Sensitivity analysis 4 was a repeat of the analysis of the primary outcome, accounting for a random effect for centre using a random intercept model; see Table 8.5 for the results.

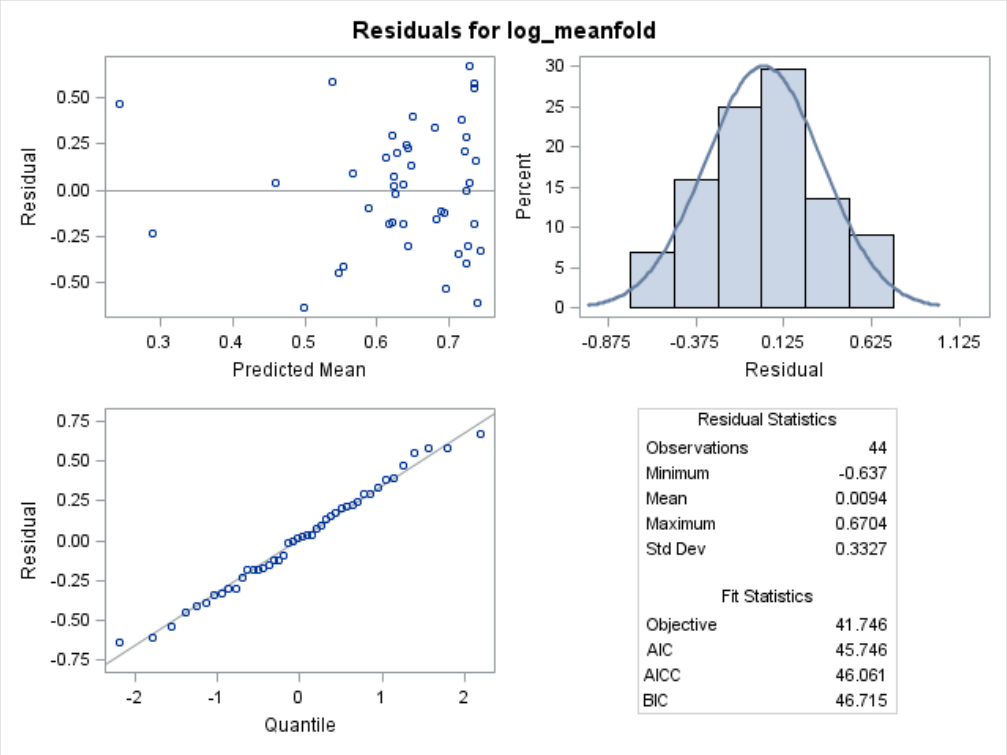
Table 8.5: Primary Outcome – Sensitivity Analysis 4: Random Intercept for Centre Mixed Model Results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	24	1.82	1.09	0.89, 1.34	0.38
Rosuvastatin	20	1.99			

*Adjusted for baseline normalised KIM-1.

Figure 8.13 shows the model diagnostics.

Figure 8.13: Panel of residual statistics for sensivity analysis 4: Random intercept for centre model



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Sensitivity analysis 4.sas*

8.1.6 Primary Outcome – Sensitivity Analysis 5

Sensitivity analysis 5 was a repeat of the analysis of the primary outcome, excluding any normalised KIM-1 results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.6 for the results.

Table 8.6: Primary Outcome – Sensitivity Analysis 5: ANCOVA results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	18	1.89	1.02	0.83, 1.24	0.85
Rosuvastatin	20	1.92			

*Adjusted for baseline normalised KIM-1.

Figure 8.14 - Figure 8.16 show the model diagnostics.

Figure 8.14: Histogram assessing normality of residuals for sensitivity analysis 5

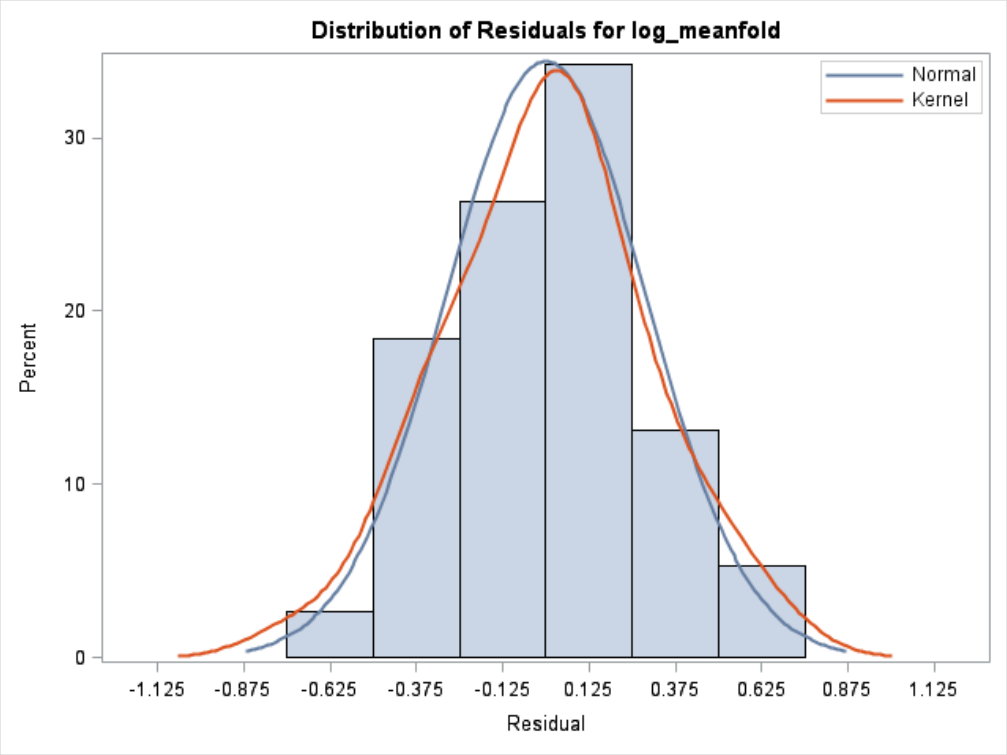


Figure 8.15: Q-Q plot assessing normality of residuals for sensitivity analysis 5

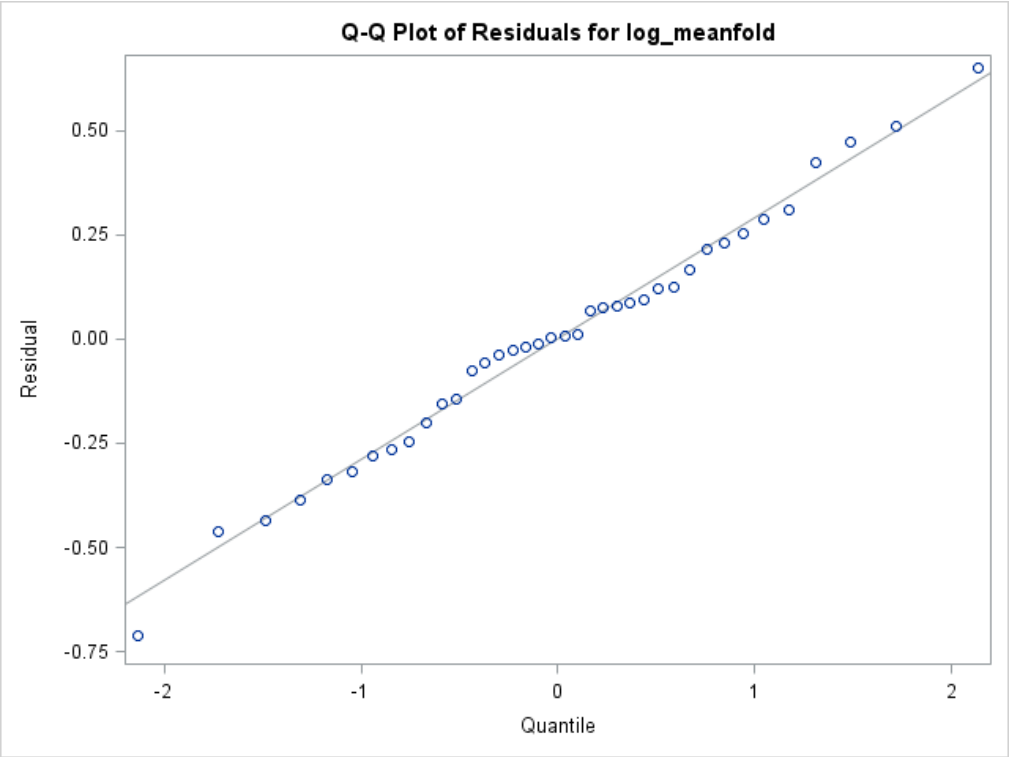
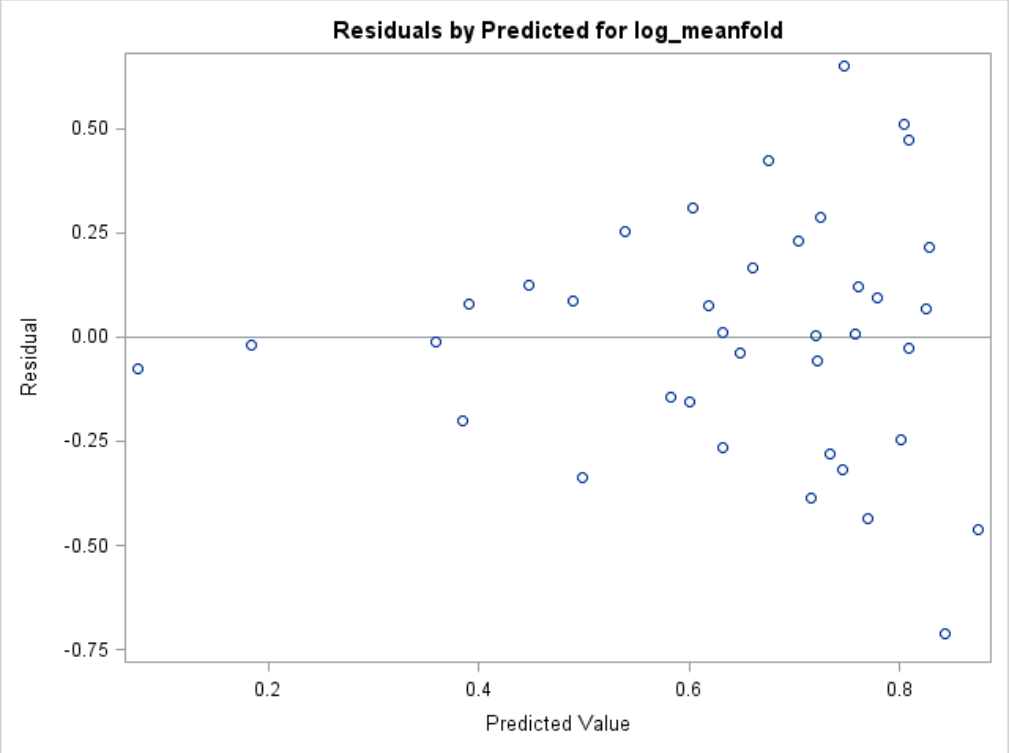


Figure 8.16: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 5



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – Sensitivity analysis 5.sas*

8.1.7 Primary Outcome – Additional Analysis: Area under the curve (AUC)

The area under the curve (AUC) of normalised KIM-1 was compared between the two treatment groups using a T-test; see Table 8.7 for the results.

Table 8.7: Primary Outcome – Additional Analysis: AUC T-test results

Treatment group	N	Mean (SD) AUC of normalised KIM-1 (ng/mgCr)	Estimated mean treatment difference	95% CI	P-value
Control	27	23.05 (33.02)	12.41	-0.89, 25.70	0.07
Rosuvastatin	21	10.65 (6.11)			

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Primary Outcome – AUC.sas*

8.1.8 Change in serum concentration of creatinine and eGFR during tobramycin exposure between the rosuvastatin group and control group

Figure 8.17: Individual profile plots of serum creatinine – control group

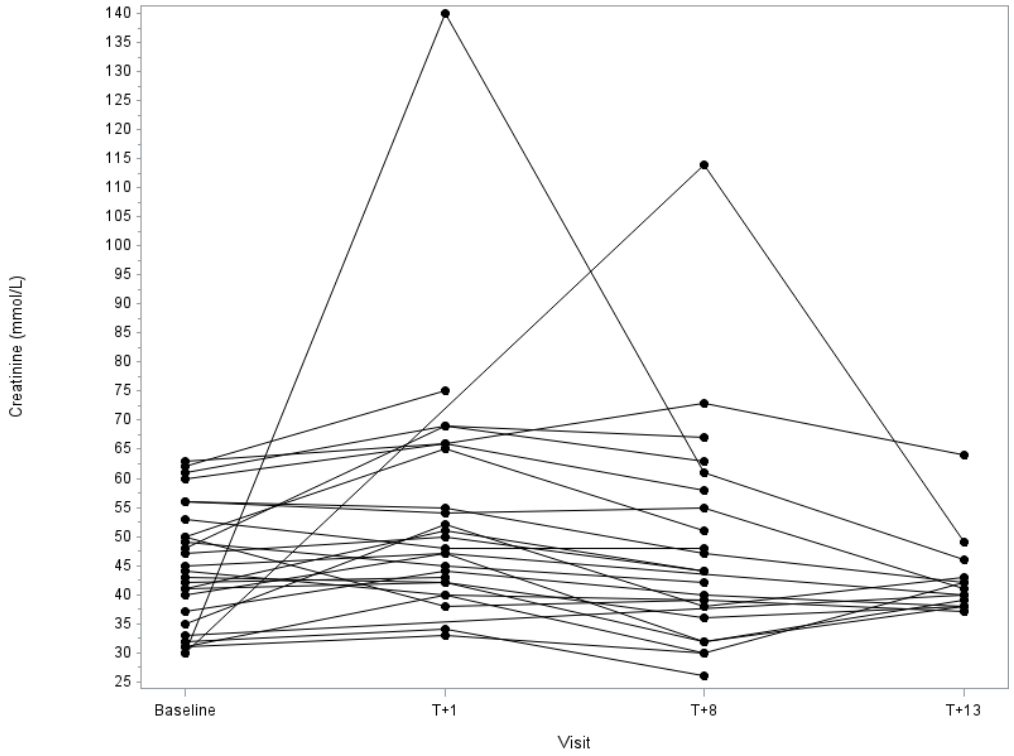


Figure 8.18: Individual profile plots of serum creatinine – rosuvastatin group

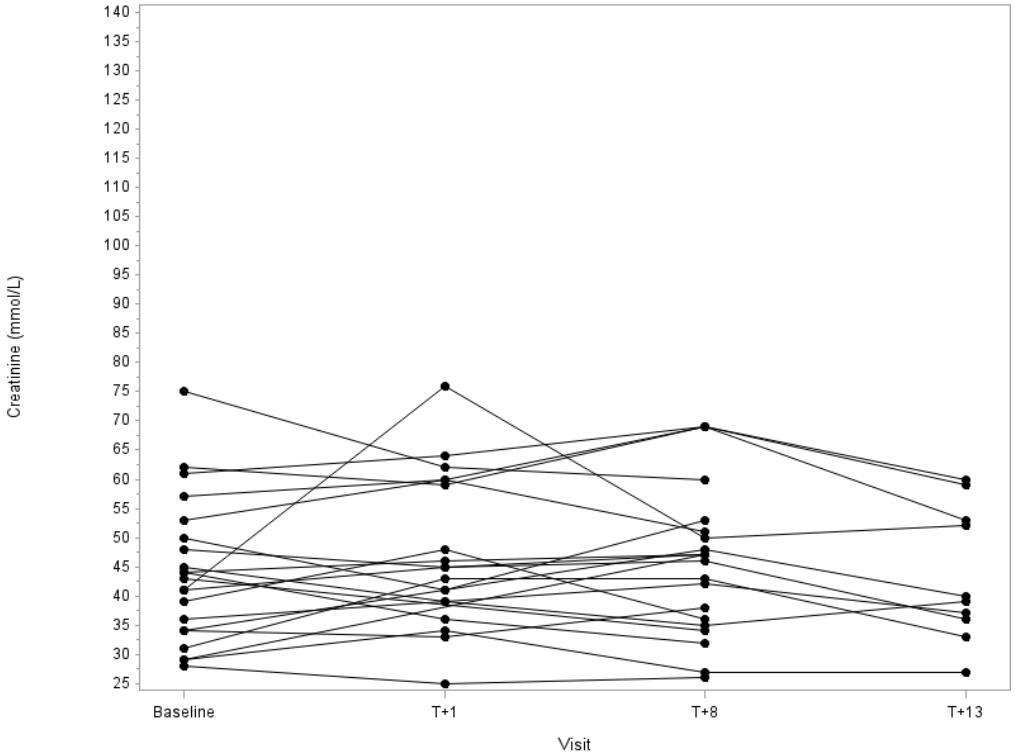
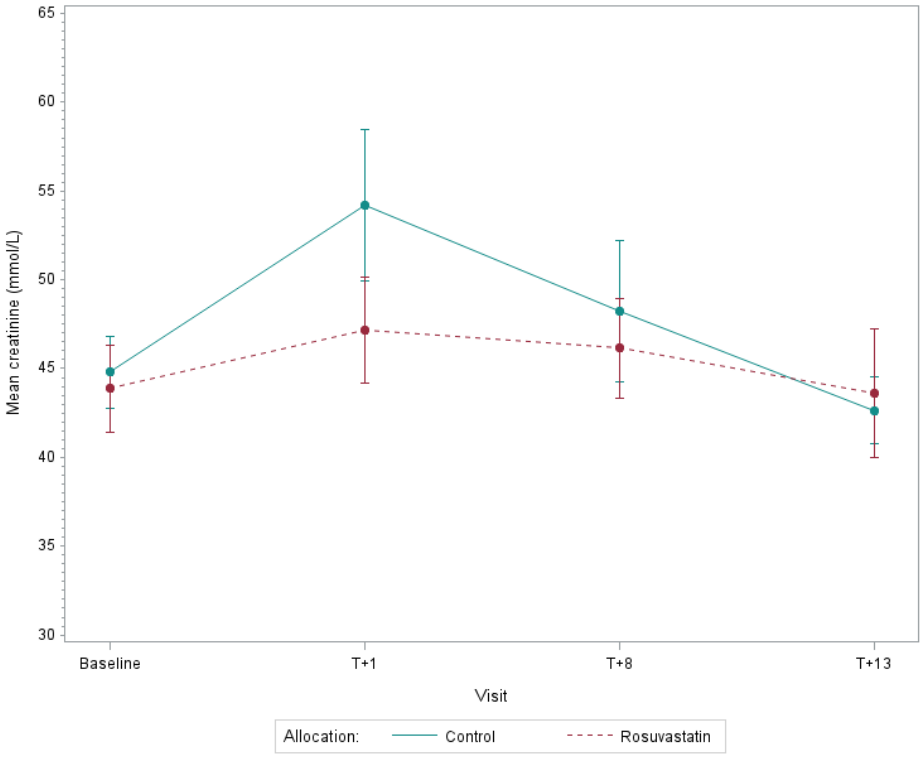


Figure 8.19: Mean profile plots of serum creatinine by treatment group



A random intercept model including an interaction term between time and treatment was used to compare serum concentration of creatinine during tobramycin exposure between the treatment groups at each of the specified time points; see Table 8.8 for the results.

Table 8.8: Difference in serum concentration of creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean creatinine (mmol/L)	N	Estimated mean creatinine (mmol/L)				
Baseline	27	44.81	23	43.87	-	-	-	0.43
T+1	25	54.55	19	46.67	-7.89	-16.53, 0.76	0.07	
T+8	23	48.23	21	46.09	-2.14	-10.73, 6.45	0.62	
T+13/last treatment	14	42.84	10	42.00	-0.83	-11.82, 10.15	0.88	
Overall	**27**	**47.61**	**23**	**44.66**	**-2.95**	**-9.61, 3.71**	**0.38**	

A sensitivity analysis was undertaken excluding any serum creatinine results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.9 for the results.

Table 8.9: Sensitivity Analysis: Difference in serum concentration of creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean creatinine (mmol/L)	N	Estimated mean creatinine (mmol/L)				
Baseline	27	44.81	23	43.87	-	-	-	0.09
T+1	24	50.15	18	44.98	-5.17	-11.84, 1.51	0.13	
T+8	22	45.21	21	46.04	0.84	-5.79, 7.46	0.80	
T+13/last treatment	14	45.00	10	41.83	-3.16	-10.65, 4.32	0.40	
Overall	**27**	**46.29**	**23**	**44.18**	**-2.11**	**-8.12, 3.90**	**0.48**	

Figure 8.20: Individual profile plots of serum eGFR – control group

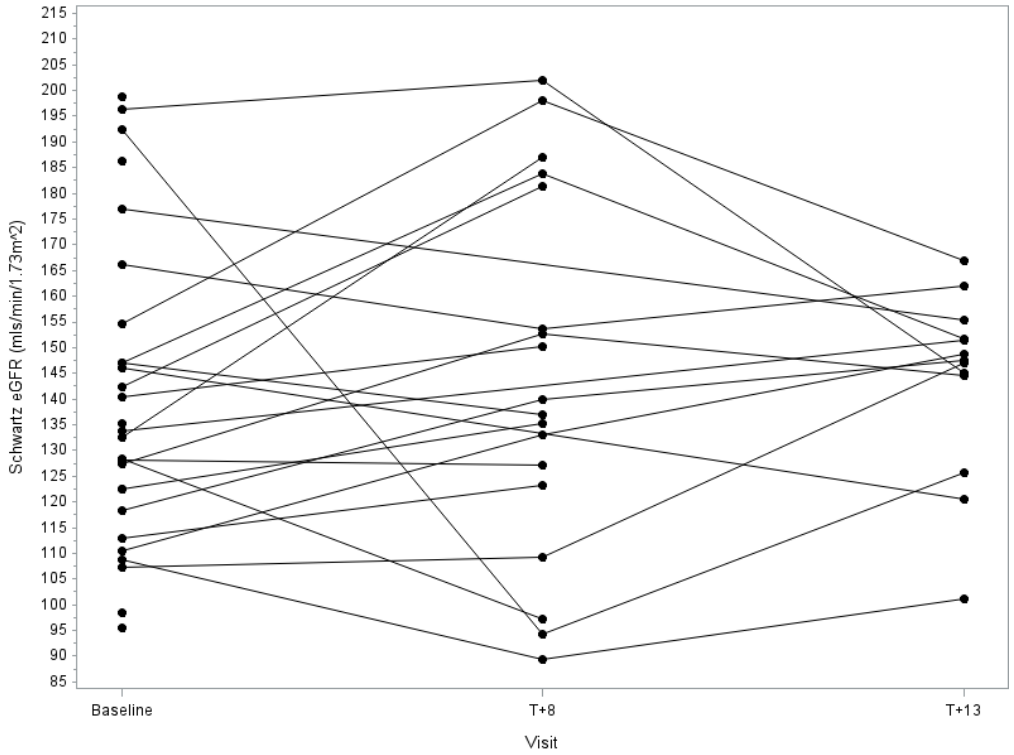


Figure 8.21: Individual profile plots of serum eGFR – rosuvastatin group

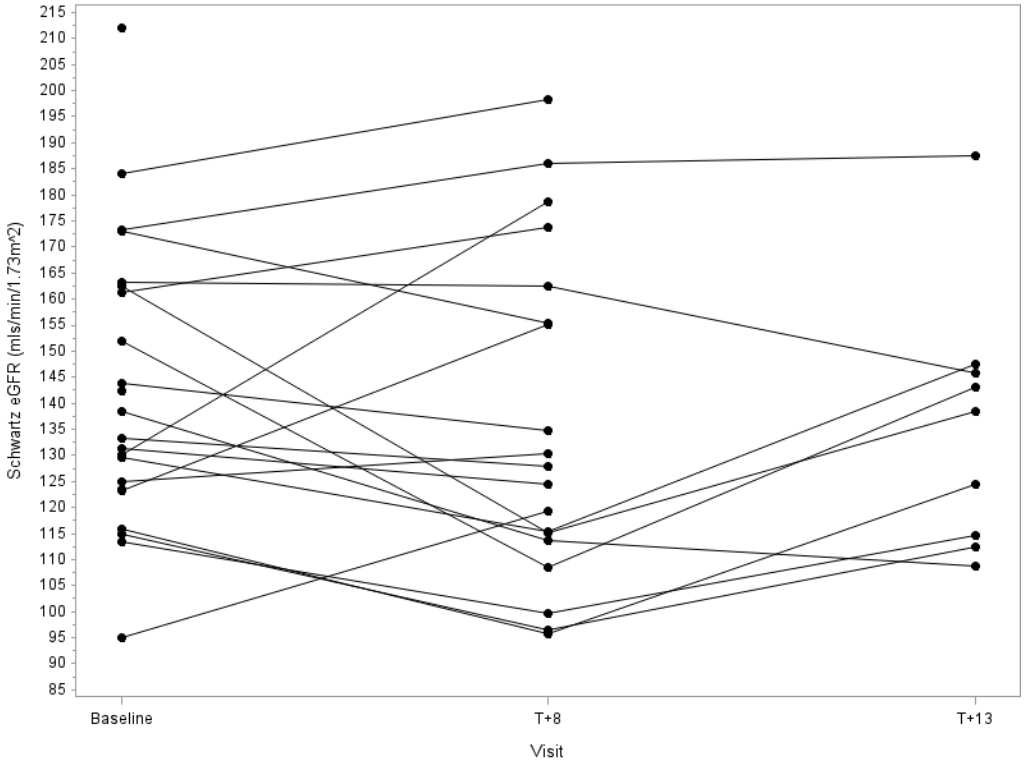
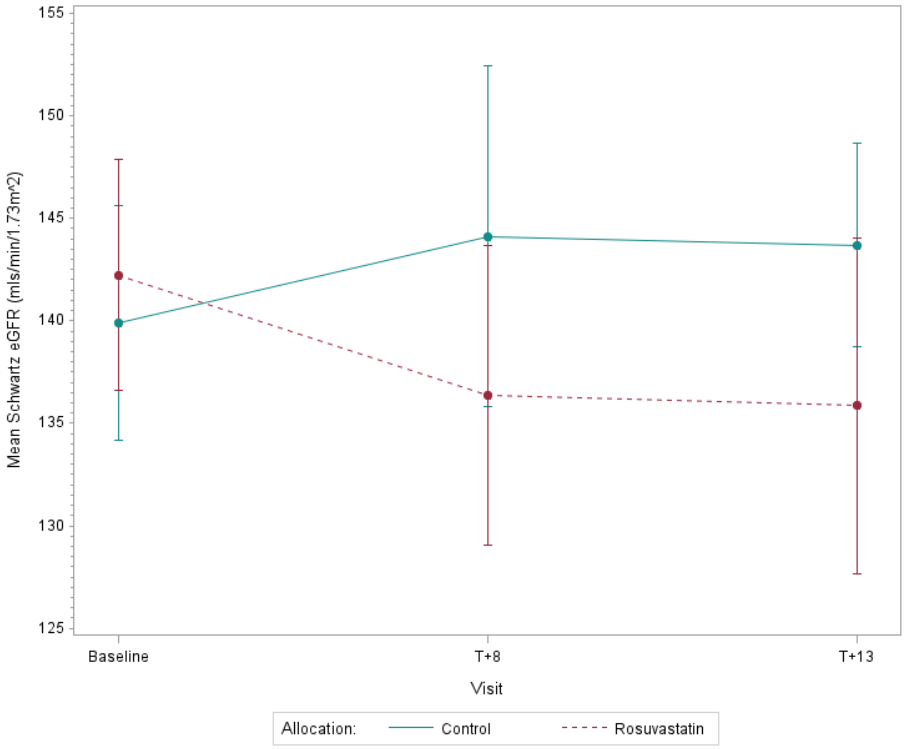


Figure 8.22: Mean profile plots of serum eGFR by treatment group



A random intercept model including an interaction term between time and treatment was used to compare serum concentration of eGFR during tobramycin exposure between the treatment groups at each of the specified time points; see Table 8.10 for the results.

Table 8.10: Difference in serum concentration of eGFR during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean eGFR (mls/min/1.73m^2)	N	Estimated mean eGFR (mls/min/1.73m^2)				
Baseline	27	139.90	23	142.21	-	-	-	0.55
T+8	23	144.84	21	137.46	-7.37	-25.84, 11.09	0.43	
T+13/last treatment	14	141.30	10	142.09	0.78	-21.89, 23.45	0.95	
Overall	**27**	**142.01**	**23**	**140.59**	**-1.43**	**-16.64, 13.78**	**0.85**	

A sensitivity analysis was undertaken excluding any eGFR results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.11 for the results.

Table 8.11: Sensitivity Analysis: Difference in serum concentration of eGFR during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean eGFR (mls/min/1.73m^2)	N	Estimated mean eGFR (mls/min/1.73m^2)				
Baseline	27	139.90	22	139.03	-	-	-	0.63
T+8	18	144.81	19	135.79	-9.01	-26.96, 8.92	0.32	
T+13/last treatment	13	141.38	9	140.27	-1.11	-23.25, 21.03	0.92	
Overall	**27**	**142.03**	**22**	**138.37**	**-3.67**	**-14.36, 11.03**	**0.62**	

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in serum.sas*

8.1.9 Difference in other urinary and plasma biomarkers of renal injury during tobramycin exposure between the rosuvastatin treated group and the control group

Figure 8.23: Individual profile plots of NGAL – control group

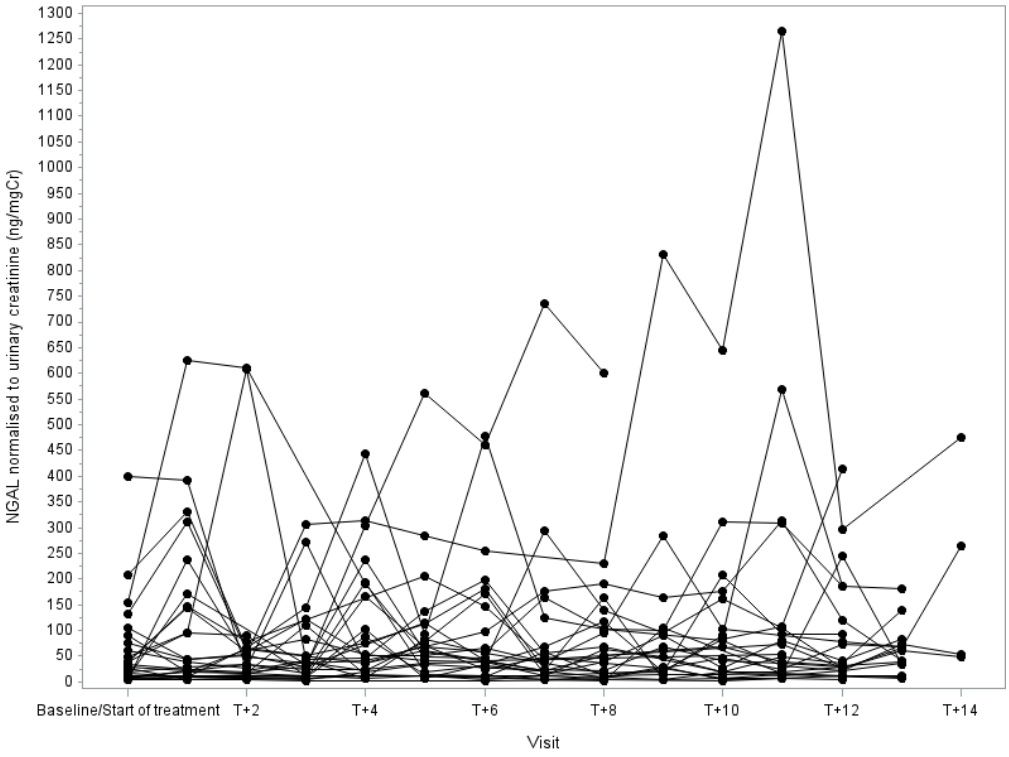


Figure 8.24: Individual profile plots of NGAL – rosuvastatin group

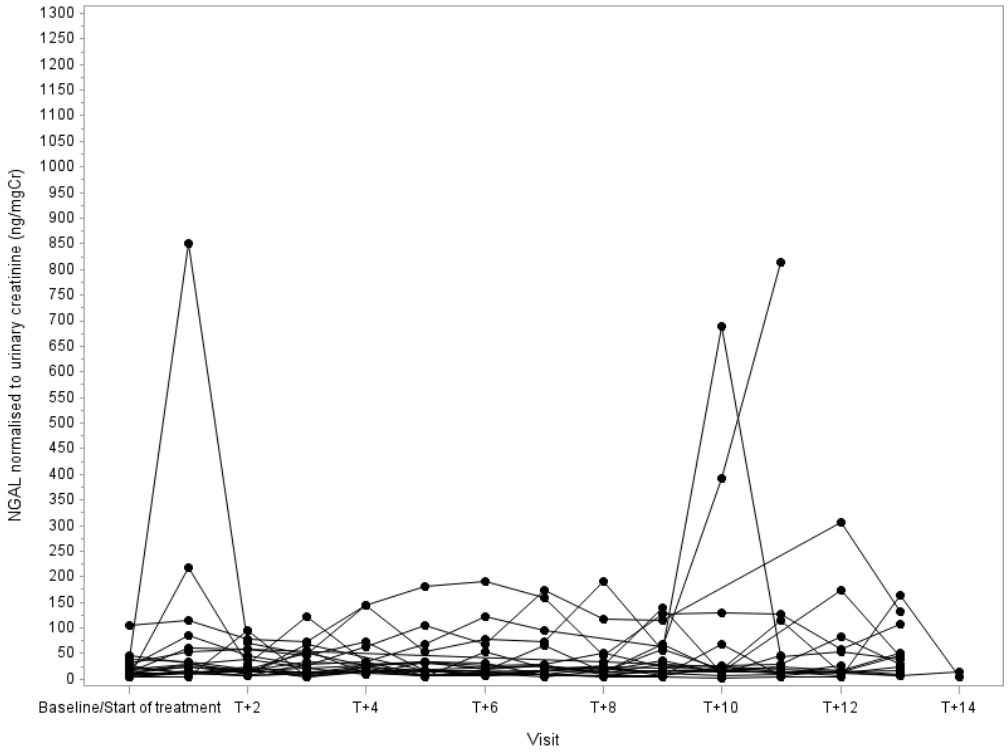
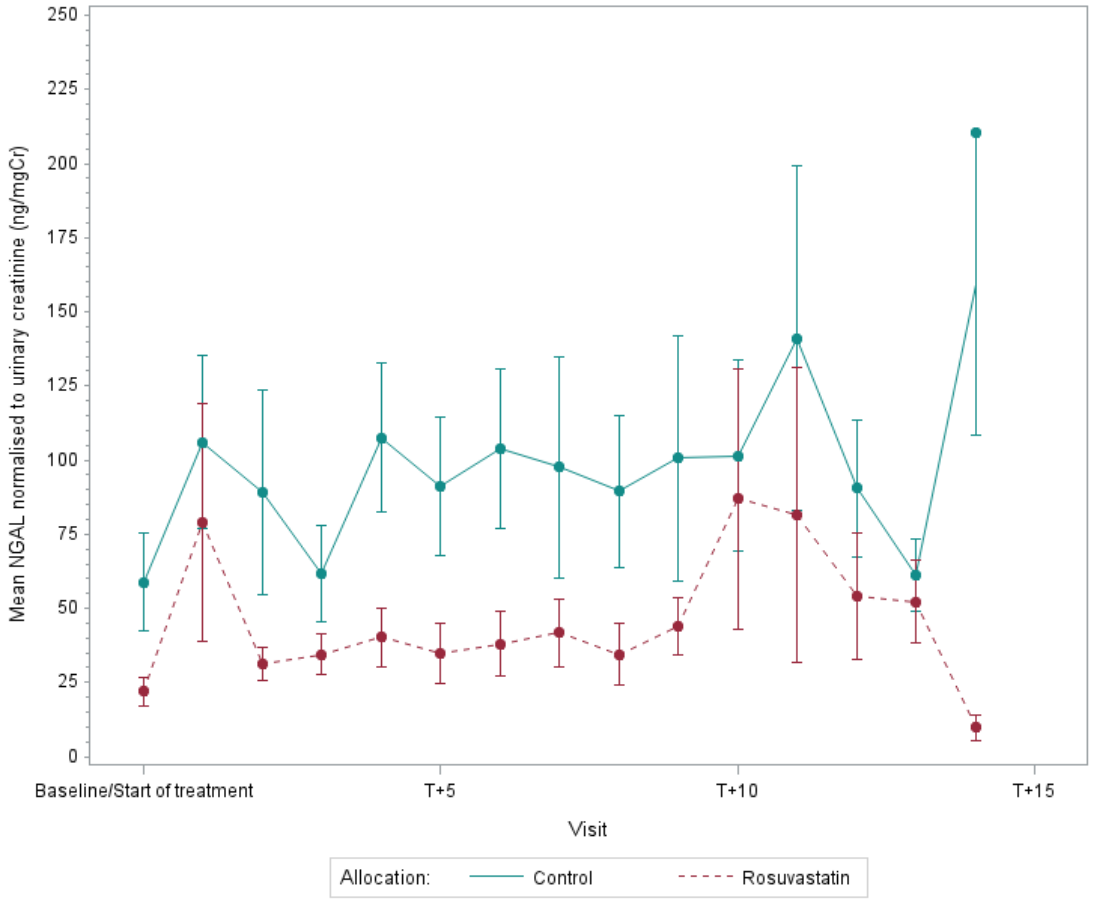


Figure 8.25: Mean profile plots of NGAL by treatment group



A random intercept model including an interaction term between time and treatment was used to compare NGAL during tobramycin exposure between the treatment groups at each of the specified time points; see Table 8.12 for the results.

Table 8.12: Difference in NGAL normalised to urinary creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean normalised NGAL (ng/mgCr)	N	Estimated mean normalised NGAL (ng/mgCr)				
Baseline/T0	27	58.78	21	21.94	-	-	-	>0.99
T+1	27	105.92	21	79.03	-26.89	-100.25, 46.47	0.47	
T+2	24	83.18	21	31.33	-51.85	-127.19, 23.49	0.18	
T+3	24	66.82	19	33.60	-33.22	-109.60, 43.16	0.39	
T+4	23	100.14	18	38.47	-61.67	-139.47, 16.13	0.12	
T+5	25	86.73	19	33.88	-52.85	-128.71, 23.01	0.17	
T+6	24	97.70	19	37.15	-60.55	-136.93, 15.83	0.12	
T+7	20	109.27	19	40.46	-68.81	-147.64, 10.02	0.09	
T+8	24	92.43	19	39.02	-53.41	-129.79, 22.96	0.17	
T+9	20	111.59	19	42.35	-69.24	-148.11, 9.64	0.09	
T+10	21	110.65	17	87.44	-23.22	-103.20, 56.76	0.57	
T+11	23	152.56	16	81.02	-71.55	-151.39, 8.29	0.08	
T+12	22	100.16	15	54.86	-45.30	-126.87, 36.27	0.28	
T+13	15	88.28	13	50.59	-37.69	-127.66, 52.29	0.41	
T+14	4	162.05	2	34.51	-127.53	-316.70, 61.64	0.19	
Overall	**27**	**101.75**	**21**	**47.04**	**-54.71**	**-102.25, -7.16**	**0.02**	

A sensitivity analysis was undertaken excluding any NGAL results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.13 for the results.

Table 8.13: Sensitivity Analysis: Difference in NGAL normalised to urinary creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean normalised NGAL (ng/mgCr)	N	Estimated mean normalised NGAL (ng/mgCr)				
Baseline/T0	25	41.26	21	21.94	-	-	-	0.81
T+1	21	42.01	19	34.12	-7.89	-29.06, 13.29	0.46	
T+2	21	38.42	21	31.33	-7.09	-27.93, 13.75	0.50	
T+3	22	43.13	19	34.20	-8.93	-29.98, 12.12	0.40	
T+4	16	41.34	18	39.89	-1.45	-23.78, 20.88	0.90	
T+5	22	55.29	18	29.98	-25.31	-46.55, -4.08	0.02	
T+6	18	41.24	18	32.93	-8.31	-30.19, 13.57	0.45	
T+7	16	38.65	18	36.71	-1.94	-24.25, 20.38	0.86	
T+8	20	49.65	18	27.79	-21.86	-43.41, -0.32	0.05	
T+9	17	50.08	19	43.22	-6.86	-28.78, 15.06	0.54	
T+10	16	48.64	15	31.64	-17.00	-39.99, 6.00	0.15	
T+11	19	45.85	15	34.64	-11.21	-33.62, 11.19	0.32	
T+12	17	40.24	13	26.02	-14.23	-37.60, 9.15	0.23	
T+13	14	50.59	12	38.53	-12.06	-36.52, 12.40	0.33	
T+14	2	41.29	2	27.14	-14.15	-68.07, 39.77	0.61	
Overall	**25**	**44.51**	**21**	**32.67**	**-11.84**	**-26.96, 3.28**	**0.12**	

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in NGAL.sas*

8.1.9.1 Change from baseline to peak NGAL

An ANCOVA model was used, comparing log-transformed mean fold-change from baseline to peak NGAL between the treatment groups, controlling for the baseline normalised NGAL. The model estimates were exponentiated to be interpretable on the normal scale; see Table 8.14 for the results.

Table 8.14: NGAL – Change from baseline to peak: ANCOVA Results

Treatment group	N	Estimated geometric mean fold-change of normalised NGAL	Estimated mean treatment difference*	95% CI	P-value
Control	24	8.90	0.56	0.27, 1.15	0.11
Rosuvastatin	20	4.99			

*Adjusted for baseline normalised KIM-1.

Figure 8.26 - Figure 8.28 show the model diagnostics.

Figure 8.26: Histogram assessing normality of residuals of NGAL ANCOVA model

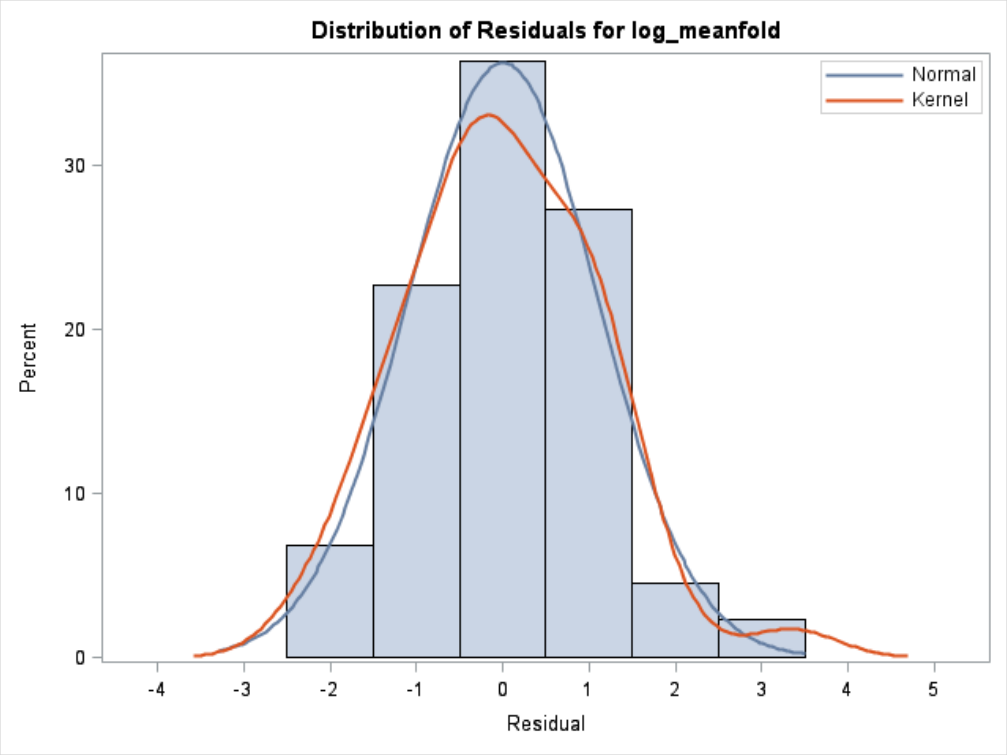


Figure 8.27: Q-Q plot assessing normality of residuals of NGAL ANCOVA model

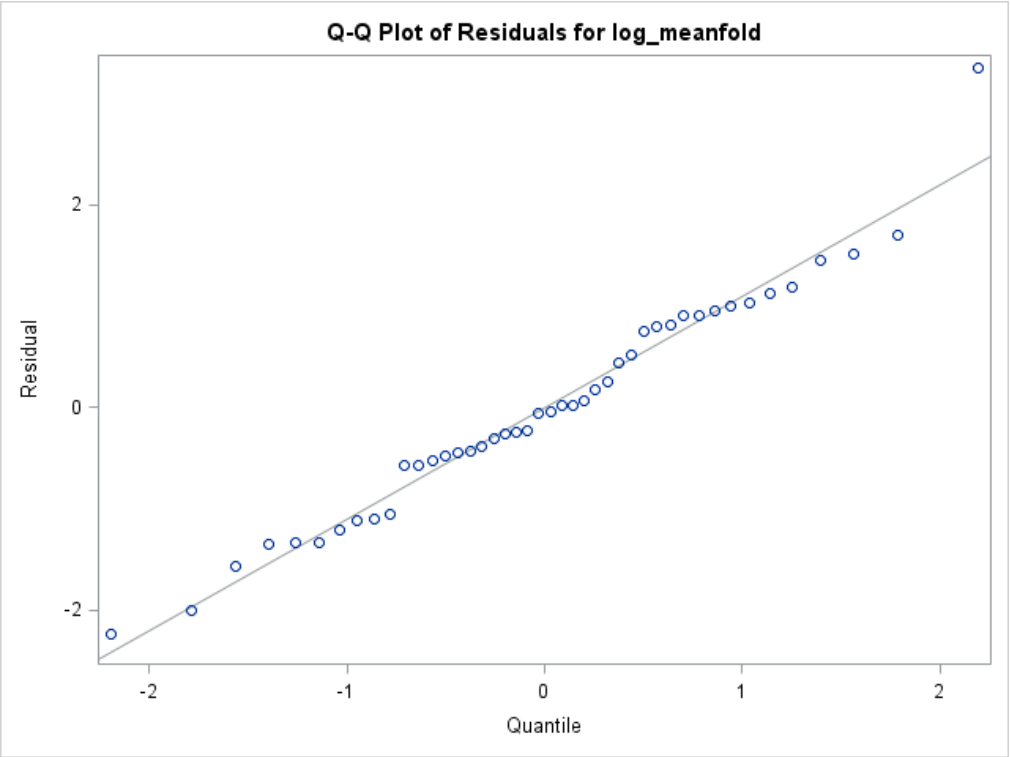
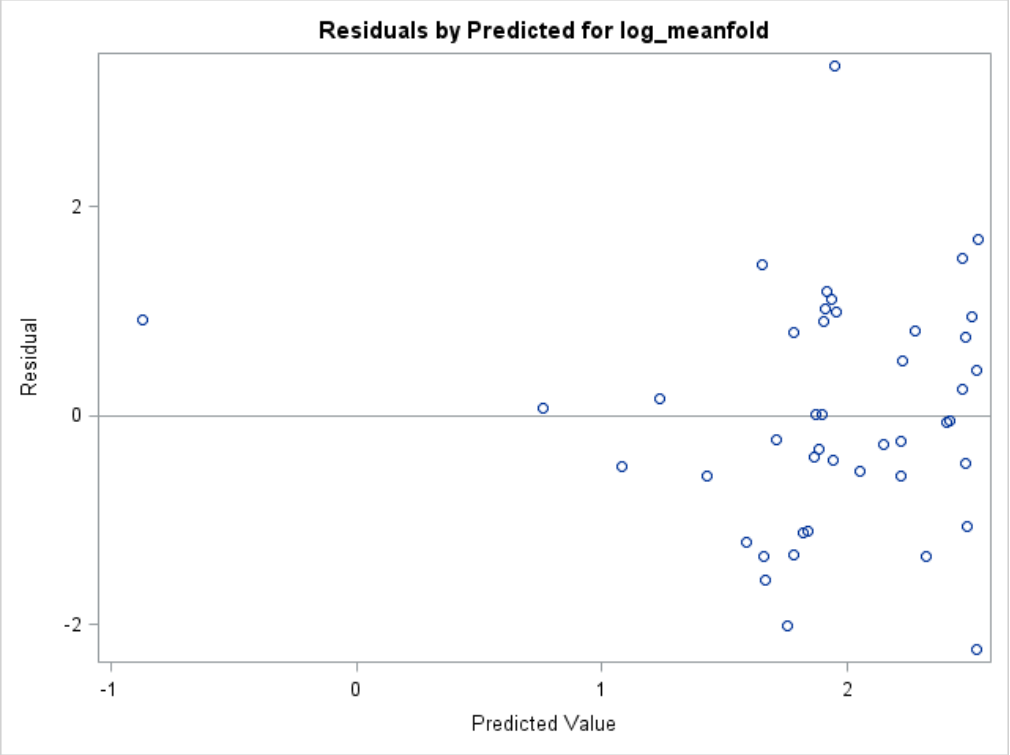


Figure 8.28: Scatter plot of residuals against fitted values assessing homoscedasticity of NGAL ANCOVA model



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in NGAL - PO.sas*

8.1.9.2 Change from baseline to peak NGAL – Sensitivity Analysis

This sensitivity analysis excluded any normalised NGAL results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.15 for the results.

Table 8.15: NGAL – Sensitivity Analysis: ANCOVA results

Treatment group	N	Estimated geometric mean fold-change of normalised KIM-1	Estimated mean treatment difference*	95% CI	P-value
Control	24	3.32	0.98	0.56, 1.72	0.95
Rosuvastatin	20	3.26			

*Adjusted for baseline normalised KIM-1.

Figure 8.29: Histogram assessing normality of residuals for NGAL sensitivity analysis

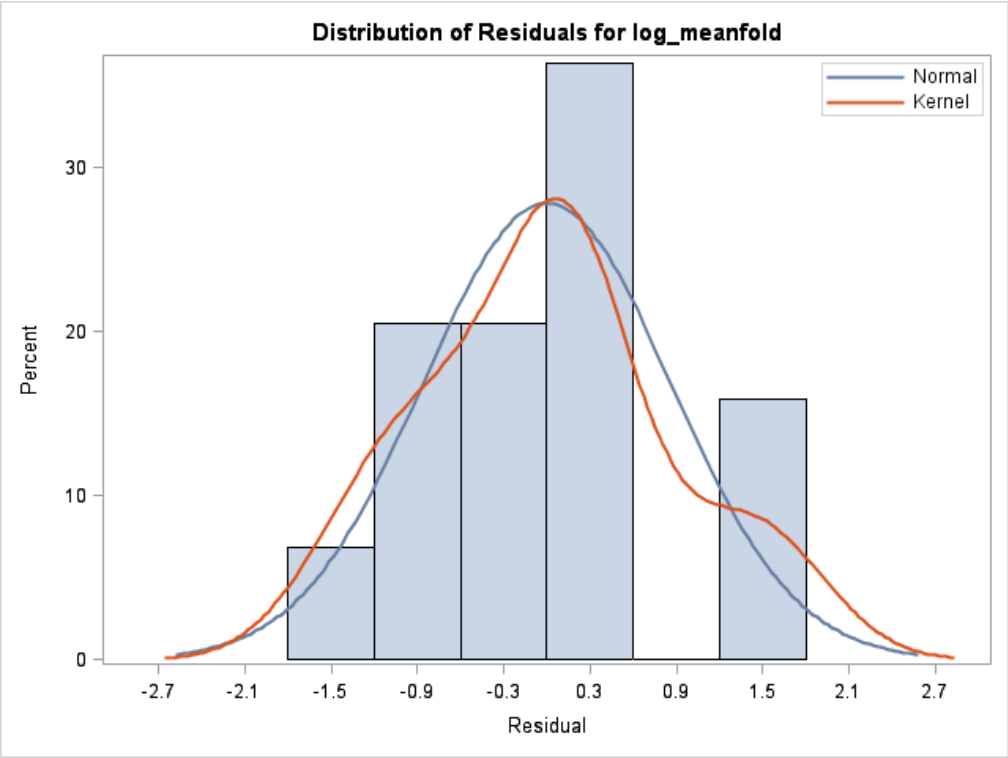


Figure 8.30: Q-Q plot assessing normality of residuals for NGAL sensitivity analysis

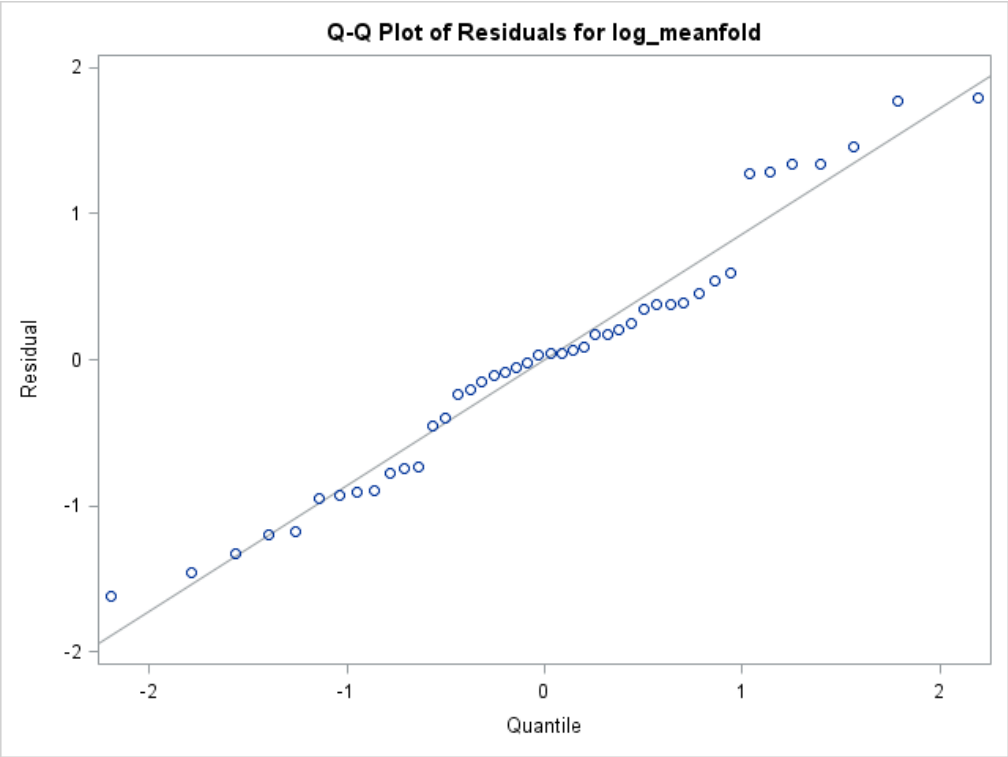
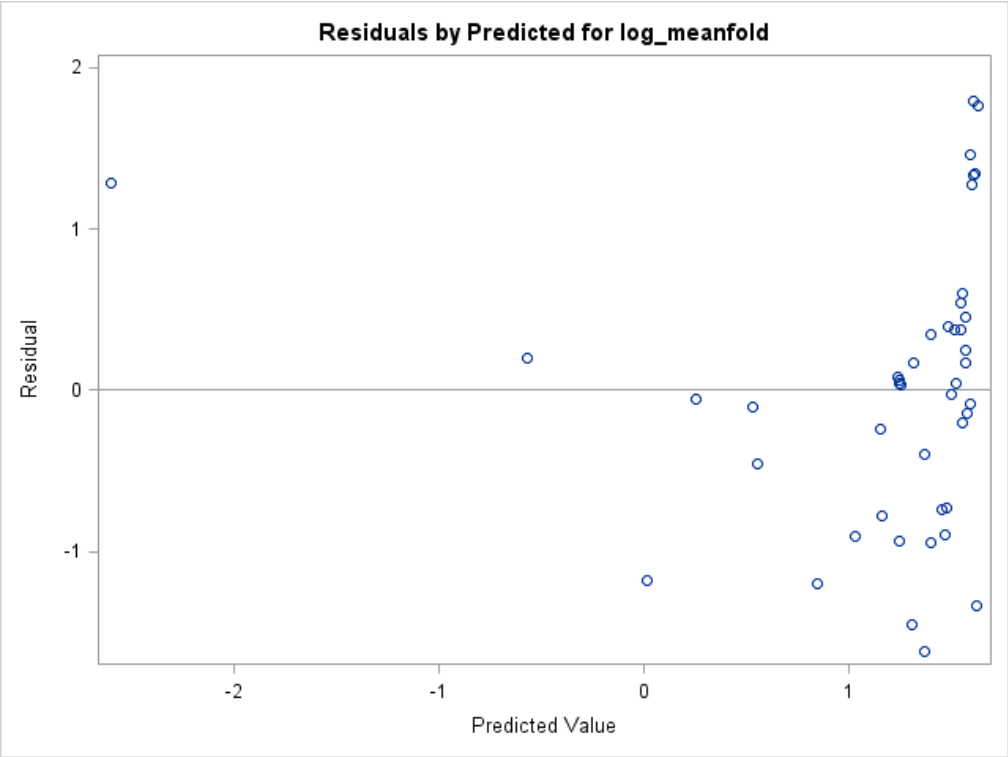


Figure 8.31: Scatter plot of residuals against fitted values assessing homoscedasticity for NGAL sensitivity analysis



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in NGAL – Sensitivity Analysis.sas*

8.1.9.3 Area Under the Curve NGAL

The area under the curve (AUC) of normalised NGAL was compared between the two treatment groups using a T-test; see Table 8.16 for the results.

Table 8.16: Additional Analysis: NGAL AUC T-test results

Treatment group	N	Mean (SD) AUC of normalised NGAL $(ng/mgCr)^2$	Estimated mean treatment difference*	95% CI	P-value
Control	27	1139.4 (1106.1)	557.8	46.5, 1069.2	0.03
Rosuvastatin	21	581.6 (630.8)			

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – NGAL - AUC.sas*

8.1.10 Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin

Tobramycin doses were taken up to three times daily. A blood sample to measure tobramycin concentrations was taken on T+1, T+8 and T+13 days (or final day of tobramycin treatment if earlier than T+13), final day of tobramycin (if later than T+13) during tobramycin exposure and at any unscheduled visits.

The non-linear mixed model did not converge and thus the analysis outlined in the Statistical Analysis Plan was not possible.

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in tobramycin.sas*

8.1.11 Difference in Forced Expiratory Volume in 1 second (FEV1) and C-Reactive Protein (CRP), between rosuvastatin treated group and the Control group to identify any pharmacodynamics interaction between rosuvastatin and the tobramycin

Figure 8.32: Individual profile plots of FEV1 – control group

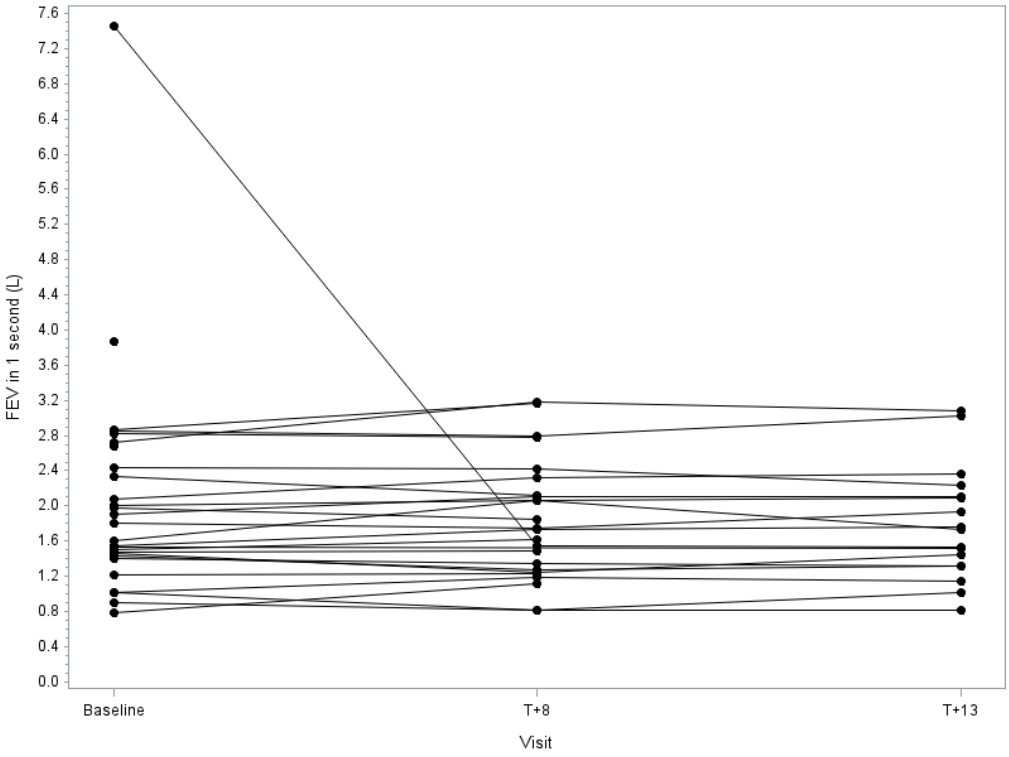


Figure 8.33: Individual profile plots of FEV1 – rosuvastatin group

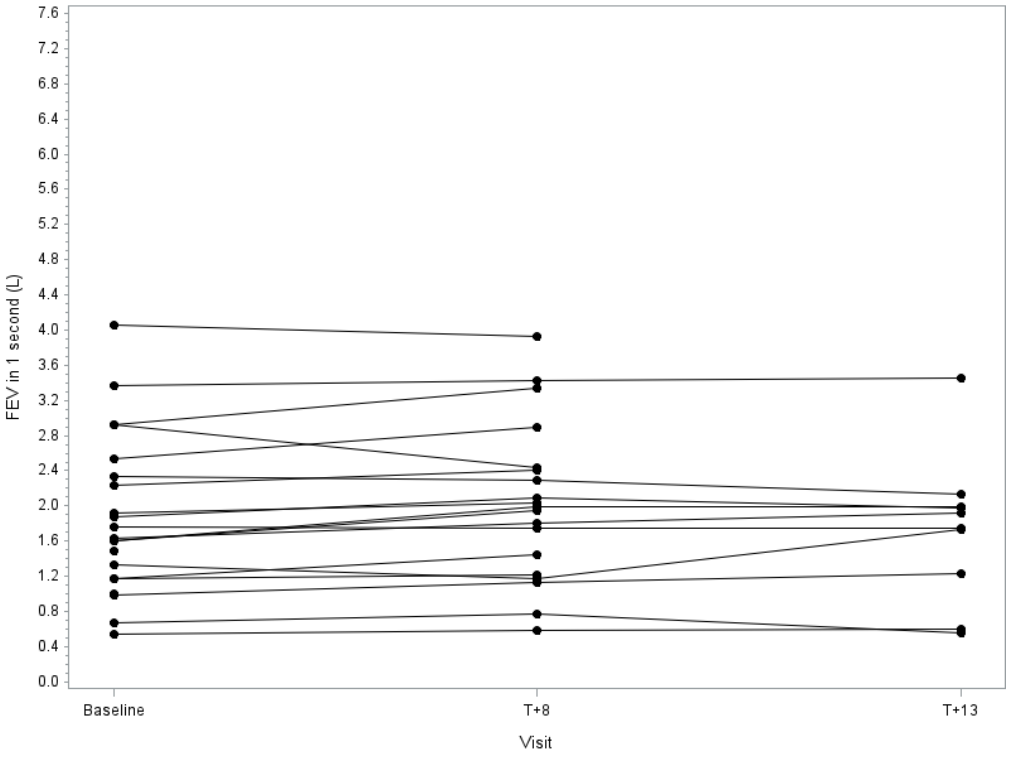
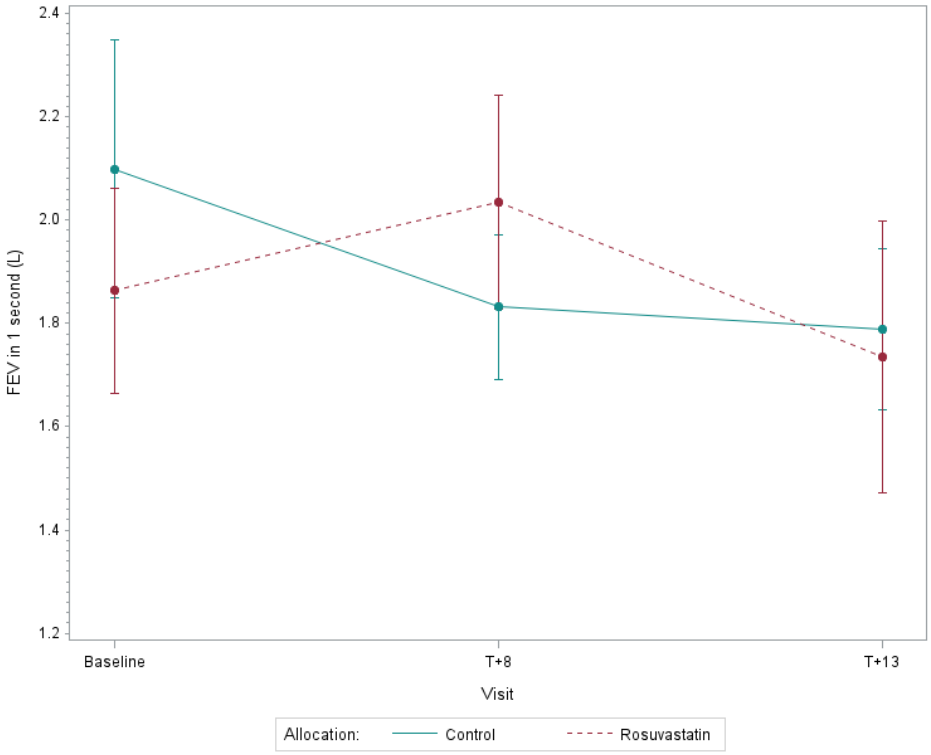


Figure 8.34: Mean profile plots of FEV in 1 second by treatment group



A random intercept model including an interaction term between time and treatment was used to compare FEV1 during tobramycin exposure between the treatment groups at each of the specified time points; see Table 8.17 for the results.

Table 8.17: Difference in FEV1 during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean FEV1 (L)	N	Estimated mean FEV1 (L)				
Baseline	27	2.10	21	1.86	-	-	-	0.34
T+8	24	1.88	19	2.00	0.12	-0.45, 0.69	0.67	
T+13/last treatment	17	1.84	10	1.94	0.10	-0.57, 0.77	0.77	
Overall	**27**	**1.94**	**21**	**1.93**	**-0.01**	**-0.50, 0.49**	**0.98**	

A sensitivity analysis was undertaken excluding any FEV1 results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.18 for the results.

Table 8.18: Sensitivity Analysis: Difference in FEV1 during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean FEV1 (L)	N	Estimated mean FEV1 (L)				
Baseline	25	1.80	20	1.75	-	-	-	0.63
T+8	24	1.85	18	1.87	0.02	-0.41, 0.45	0.93	
T+13/last treatment	17	1.87	10	1.89	0.02	-0.42, 0.46	0.93	
Overall	**25**	**1.84**	**20**	**1.84**	**-0.002**	**-0.43, 0.42**	**0.99**	

SAS program location: O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in FEV1.sas

Figure 8.35: Individual profile plots of CRP – control group

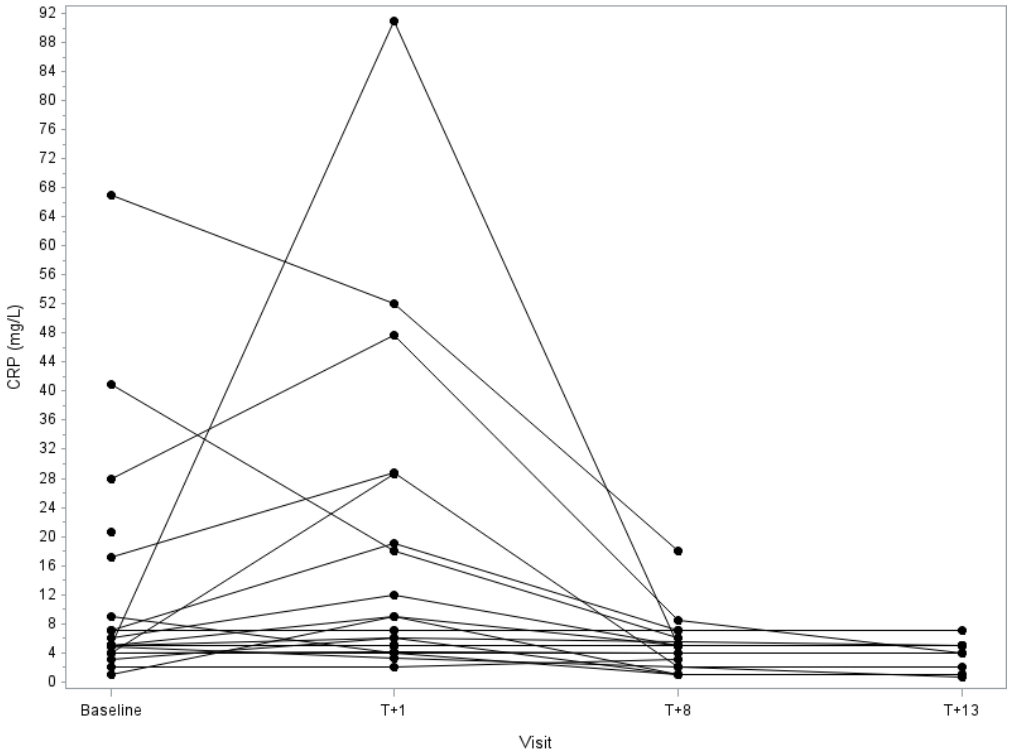


Figure 8.36: Individual profile plots of CRP – rosuvastatin group

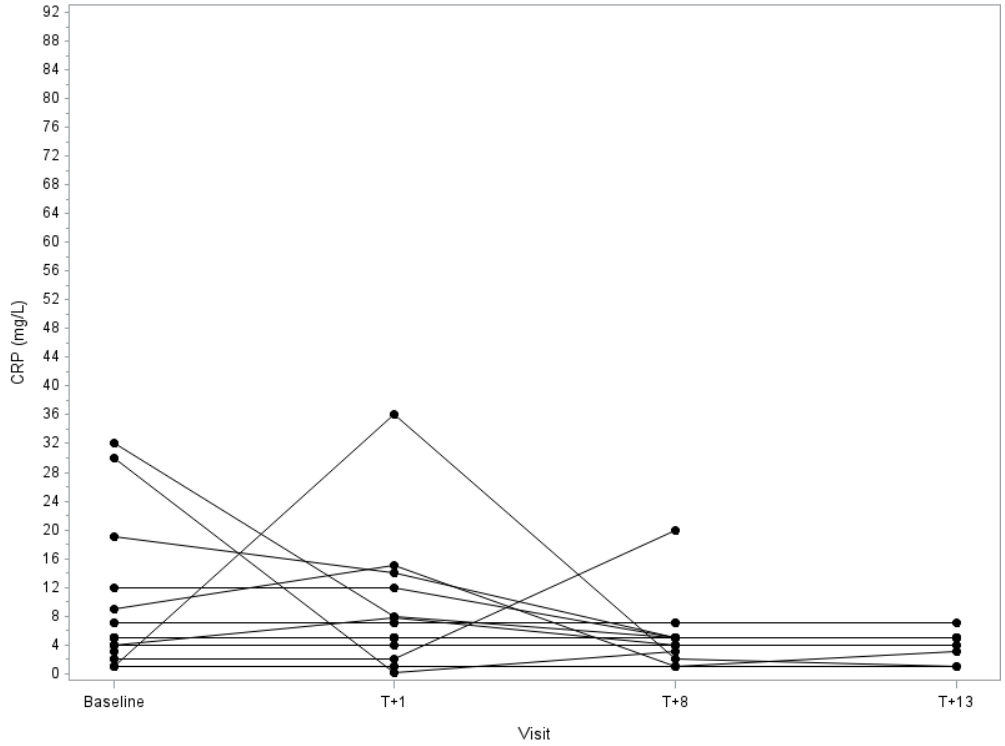
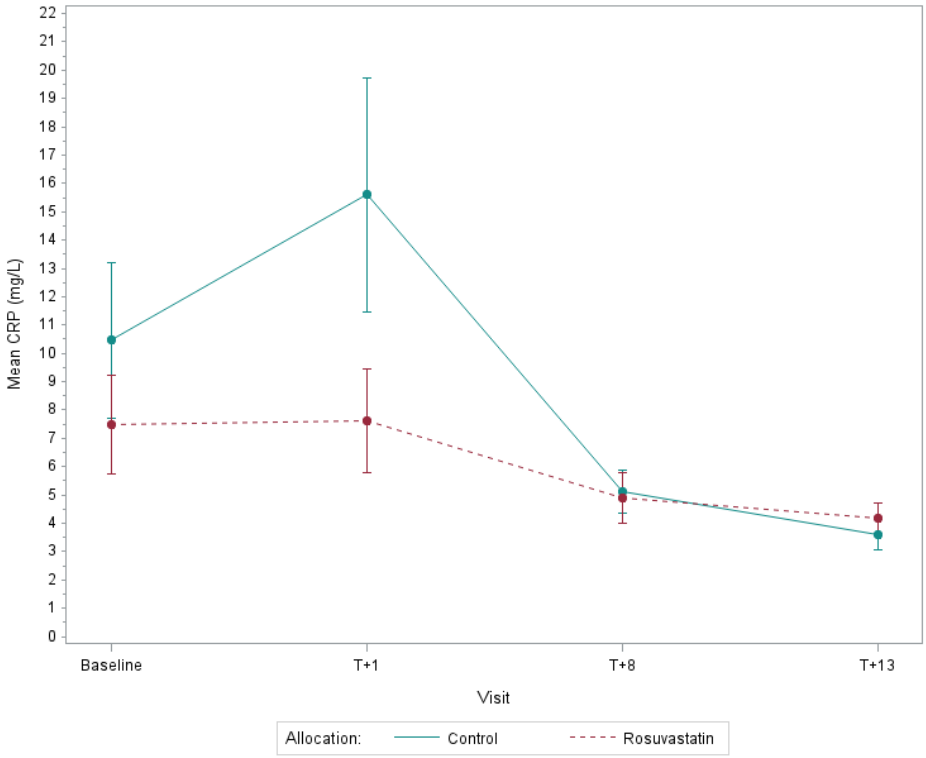


Figure 8.37: Mean profile plots of CRP by treatment group



A random intercept model including an interaction term between time and treatment was used to compare CRP during tobramycin exposure between the treatment groups at each of the specified time points; see Table 8.19 for the results.

Table 8.19: Difference in CRP during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean CRP (mg/L)	N	Estimated mean CRP (mg/L)				
Baseline	27	10.46	23	7.48	-	-	-	0.26
T+1	25	15.63	19	7.42	-8.21	-14.90, -1.53	0.02	
T+8	22	4.96	20	4.75	-0.22	-6.99, 6.56	0.95	
T+13/last treatment	14	4.95	11	3.93	-1.02	-9.68, 7.65	0.82	
Overall	**27**	**9.00**	**23**	**5.89**	**-3.11**	**-7.68, 1.46**	**0.18**	

A sensitivity analysis was undertaken excluding any CRP results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR; see Table 8.20 for the results.

Table 8.20: Sensitivity Analysis: Difference in CRP during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean CRP (mg/L)	N	Estimated mean CRP (mg/L)				
Baseline	22	4.98	19	4.21	-	-	-	
T+1	17	5.59	15	4.34	-1.24	-2.57, 0.08	0.07	
T+8	21	4.48	19	3.97	-0.51	-1.73, 0.71	0.41	0.30
T+13/last treatment	14	3.65	11	3.94	0.29	-1.17, 1.76	0.69	
Overall	**22**	**4.67**	**19**	**4.12**	**-0.56**	**-1.52, 0.41**	**0.25**	

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Change in CRP.sas*

8.1.12 Relationship between plasma rosuvastatin concentrations achieved in children randomised to the intervention group and change in urinary KIM-1

Table 8.21: Rosuvastatin concentrations and their corresponding KIM-1 values at each time point

Visit	N	Mean (SD) rosuvastatin concentration	Mean (SD) KIM-1 normalised to urinary creatinine (ng/mgCr)
T0	14	0.10 (0.36)	6.84 (5.00)
T+1	10	3.25 (4.88)	7.64 (3.46)
T+8	16	1.56 (1.13)	8.45 (3.81)
T+13	14	1.22 (1.37)	12.76 (7.45)
4 weeks following treatment cessation	13	0.33 (1.09)	7.74 (4.23)

Figure 8.38: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+1

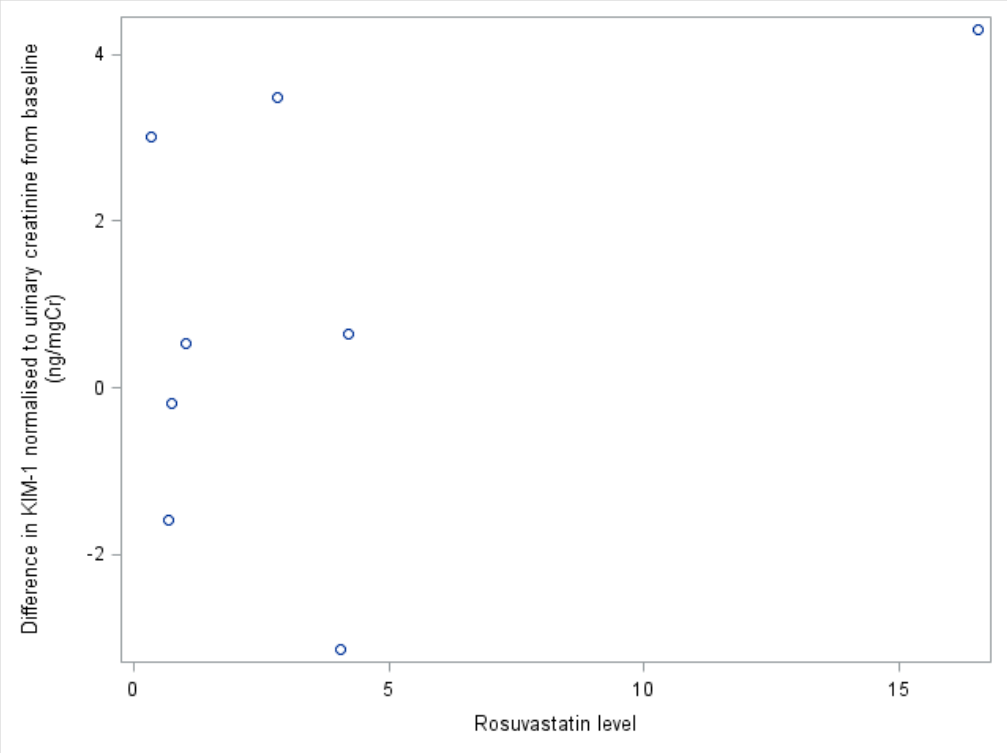


Figure 8.39: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+8

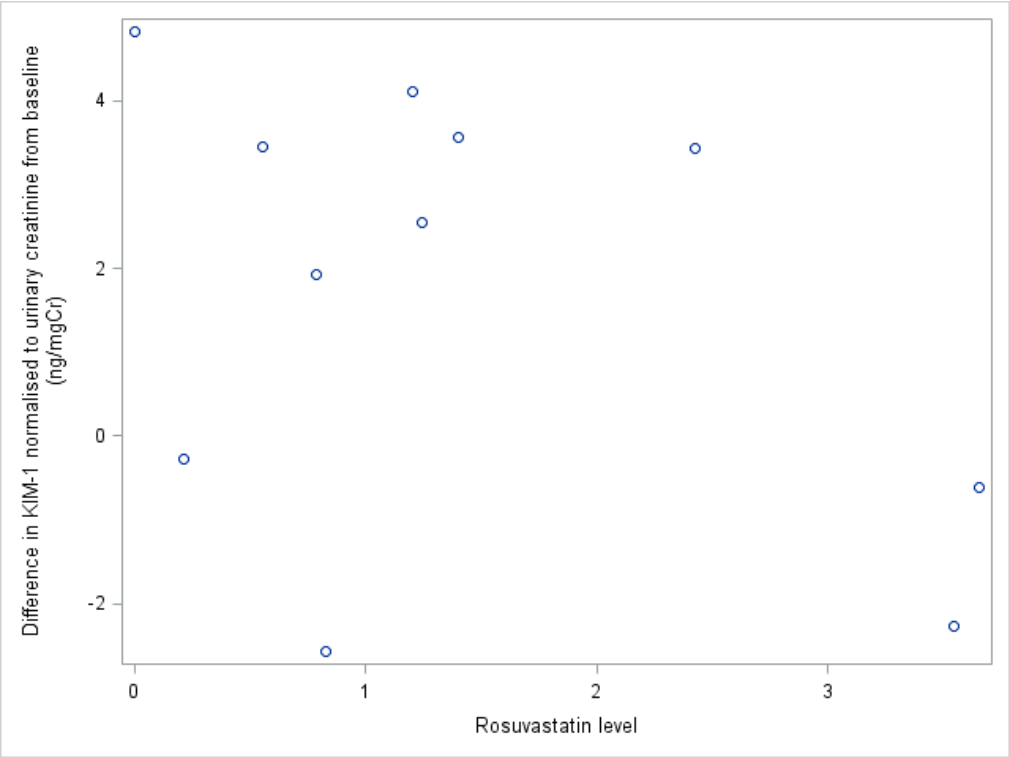


Figure 8.40: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+13

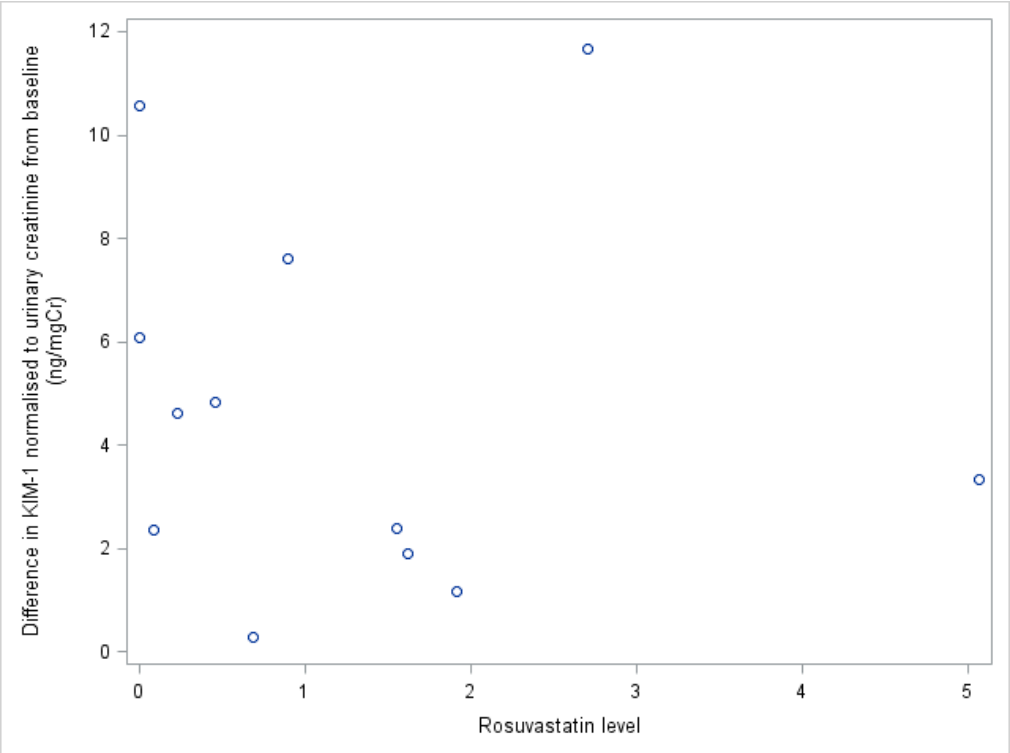
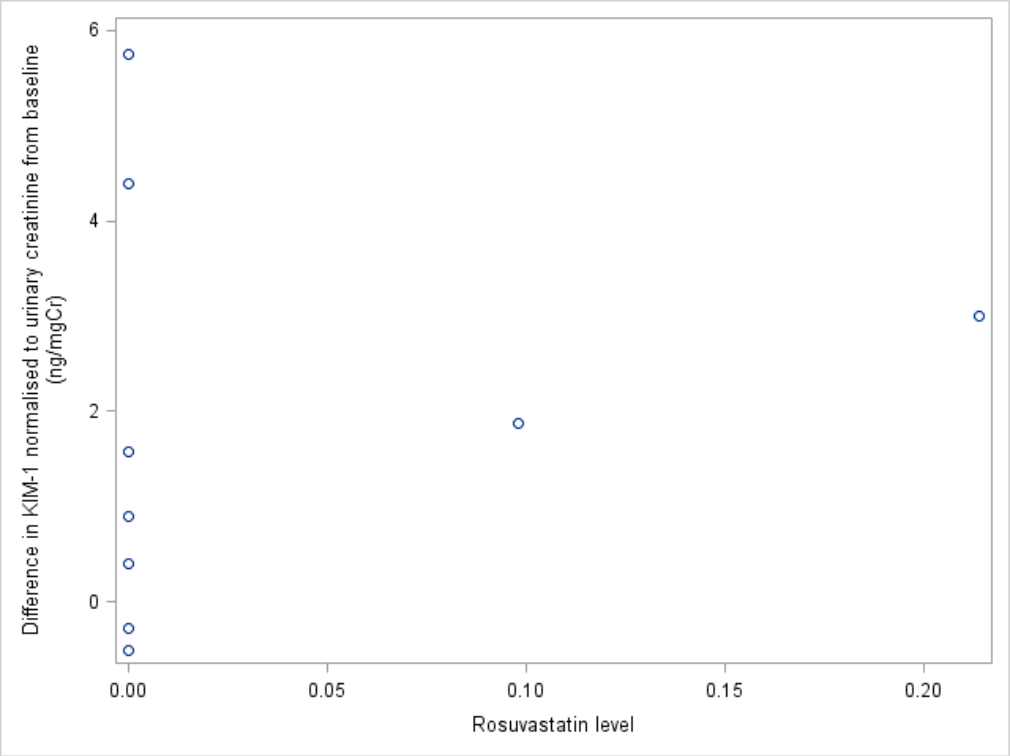


Figure 8.41: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to 4 weeks following treatment cessation



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Rosuvastatin urinary KIM-1 relationship.sas*

8.1.13 Difference in biomarkers of *Pseudomonas aeruginosa* between the rosuvastatin treated group and the control group

The specific biomarkers for this outcome have not yet been defined and therefore this analysis has not been included within the report.

9. Post-hoc Analyses

9.1 Number of baseline liver function results above the upper limit of normal (ULN) – Post-hoc analysis

Table 9.1: Number of baseline transaminase and creatine kinase results above the ULN

Result	Number of values above ULN, N (%)	
	Control	Rosuvastatin
Aspartate transaminase (iu/L)	5 (18.52%)	4 (17.39%)
Alanine transaminase (iu/L)	2 (7.41%)	4 (17.39%)
Creatine kinase (iu/L)	1 (3.70%)	2 (8.70%)

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc - OOR.sas.sas*

9.2 Association between baseline normalised KIM-1 and serum eGFR and creatinine at T+13/final day of treatment – Post-hoc analysis

Figure 9.1: Scatterplot of baseline normalised KIM-1 against serum creatinine at T+13/final day of treatment by treatment group

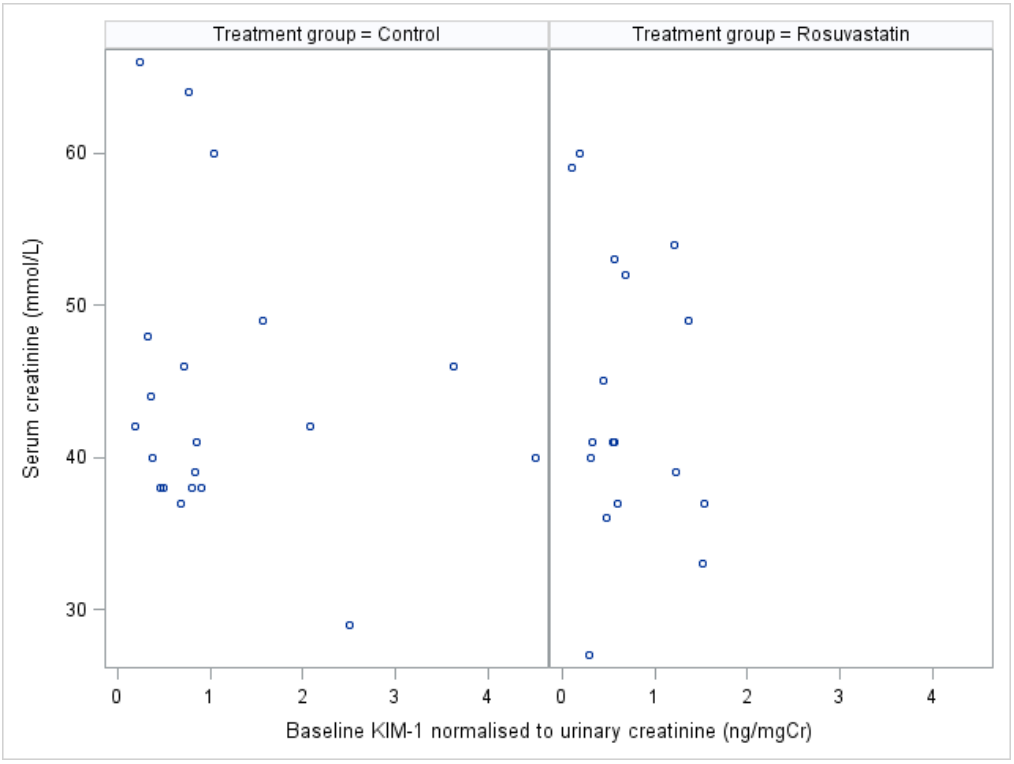


Figure 9.2: Scatterplot of baseline normalised KIM-1 against serum eGFR at T+13/final day of treatment by treatment group

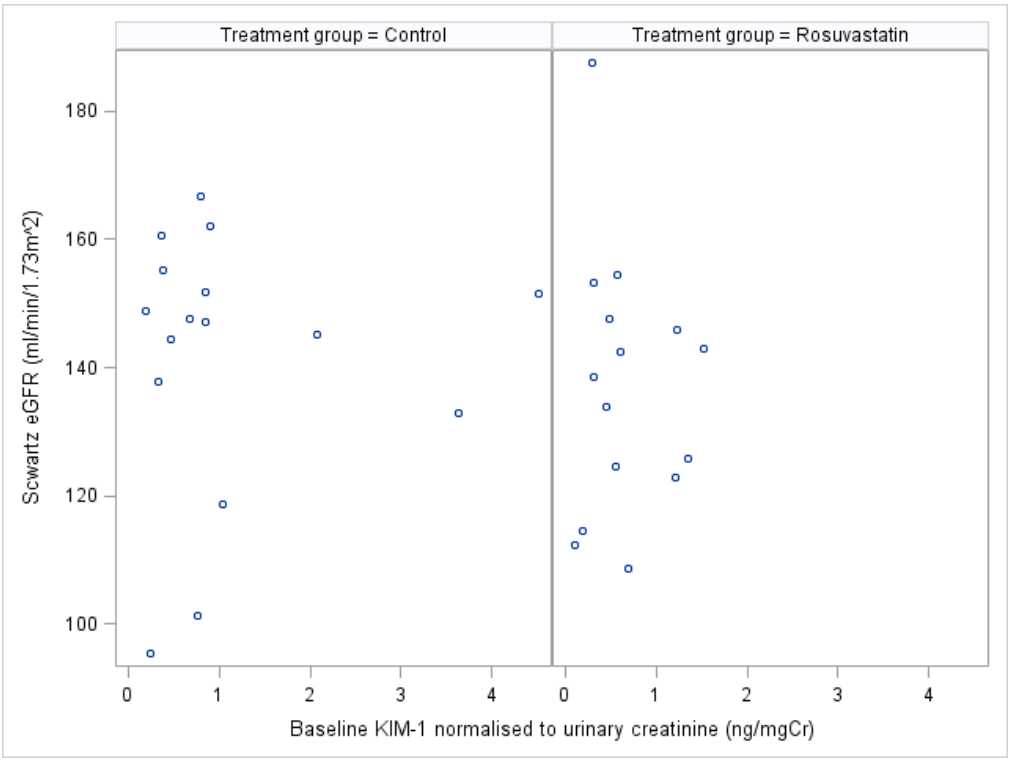


Figure 9.3 Scatterplot of baseline normalised NGAL against serum creatinine at T+13/final day of treatment by treatment group

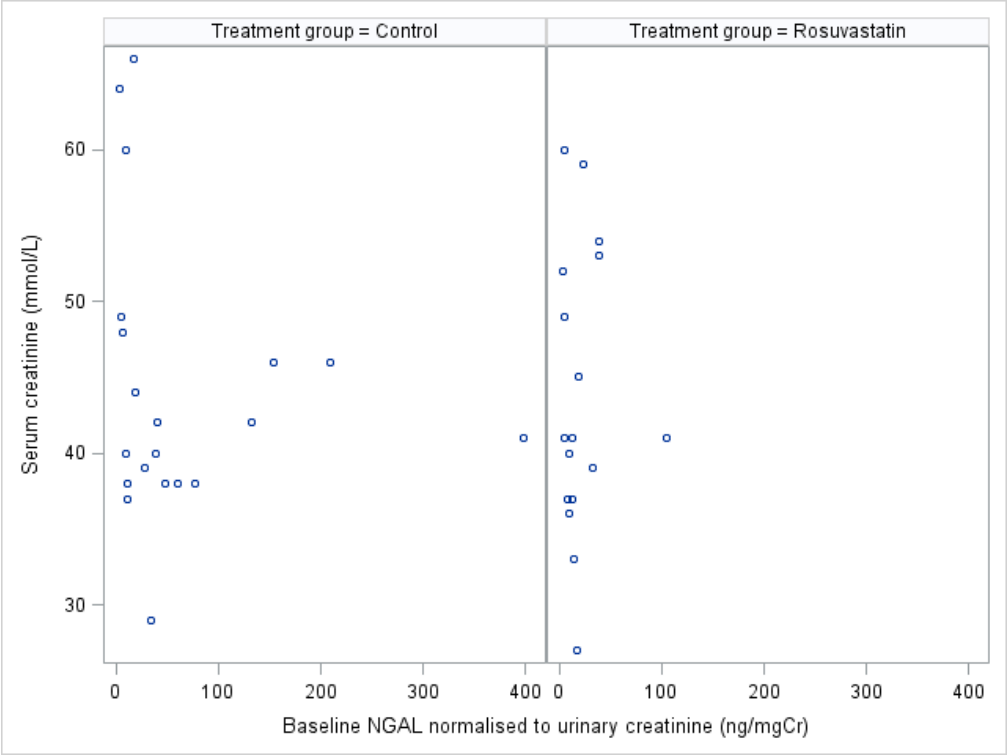


Figure 9.4: Scatterplot of baseline normalised NGAL against serum eGFR at T+13/final day of treatment by treatment group

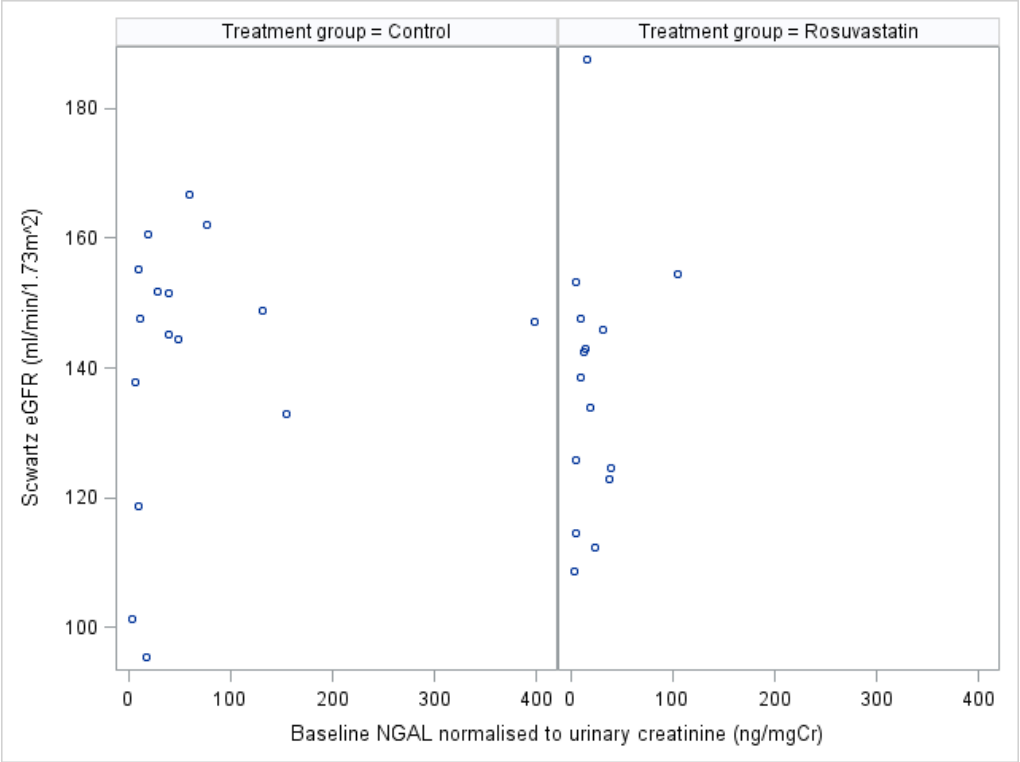


Figure 9.5: Scatterplot of baseline normalised KIM-1 against baseline normalised NGAL

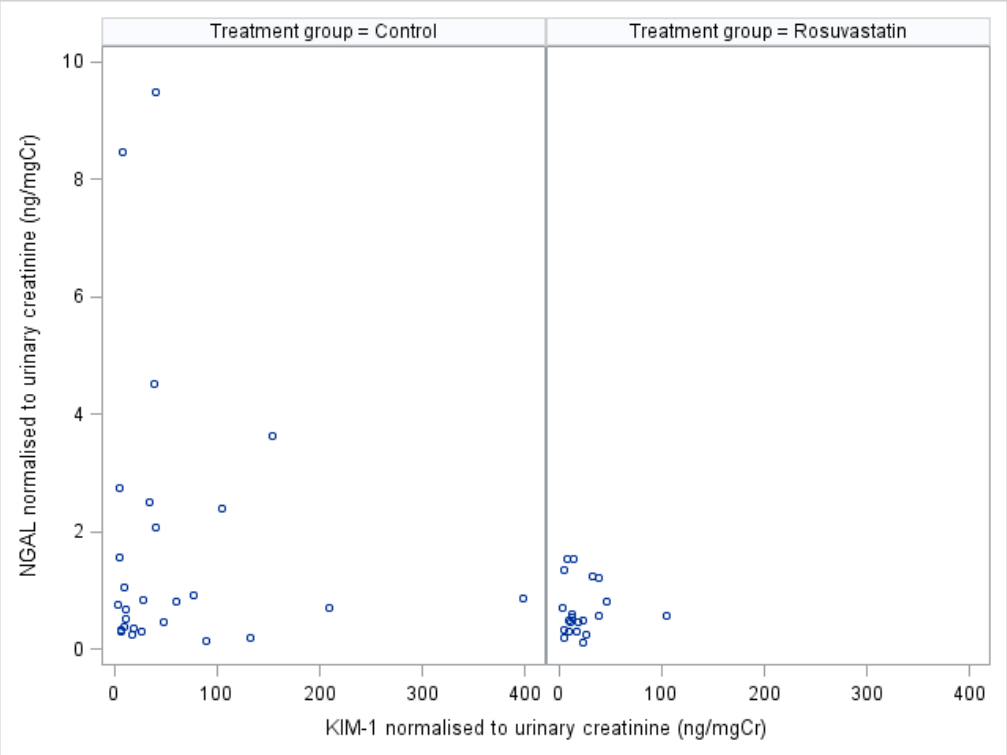


Table 9.2: Pearson's correlation between baseline normalised KIM-1 and NGAL against serum creatinine and eGFR at T+13/final day of treatment by treatment group

Comparison	Control	Rosuvastatin
Baseline KIM-1/T+13 serum creatinine	-0.19 P=0.41	-0.21 P=0.41
Baseline KIM-1/T+13 serum eGFR	0.06 P=0.83	-0.06 P=0.82
Baseline NGAL/T+13 serum creatinine	-0.15 P=0.53	0.03 P=0.91
Baseline NGAL/T+13 serum eGFR	0.17 P=0.54	0.18 P=0.51
Baseline KIM-1/Baseline NGAL	-0.08 P=0.70	0.01 P=0.97

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – Baseline KIM-1_NGAL correlations.sas*

9.3 KIM-1 Profile Plots – Post-hoc analysis

Figure 9.6: KIM-1 Individual Profile Plots: Control group

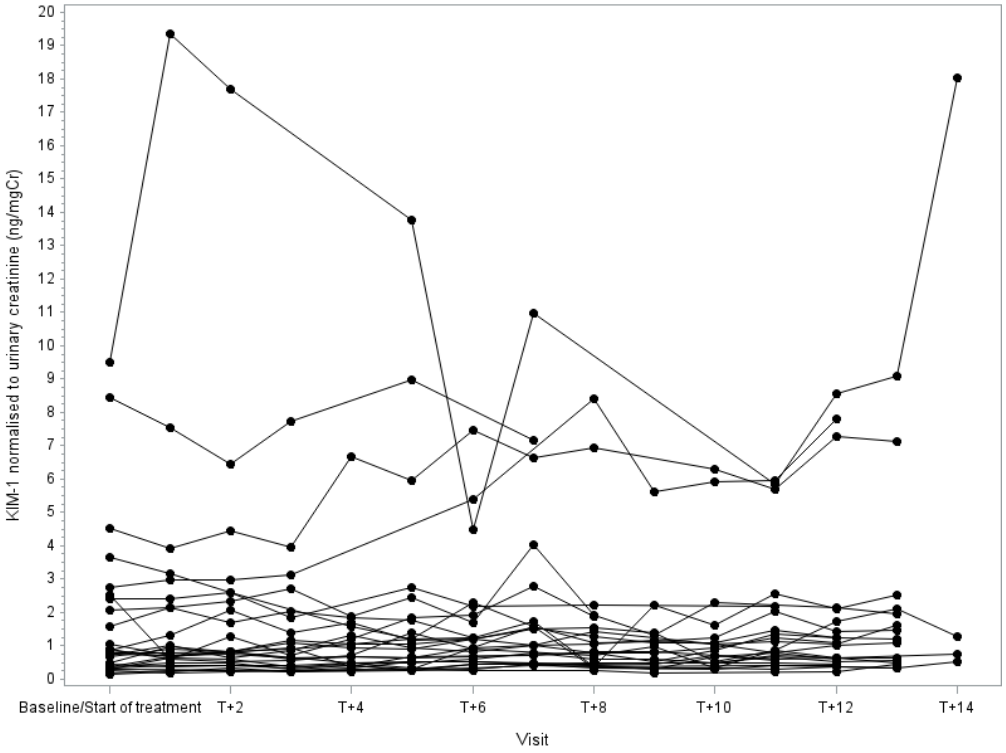
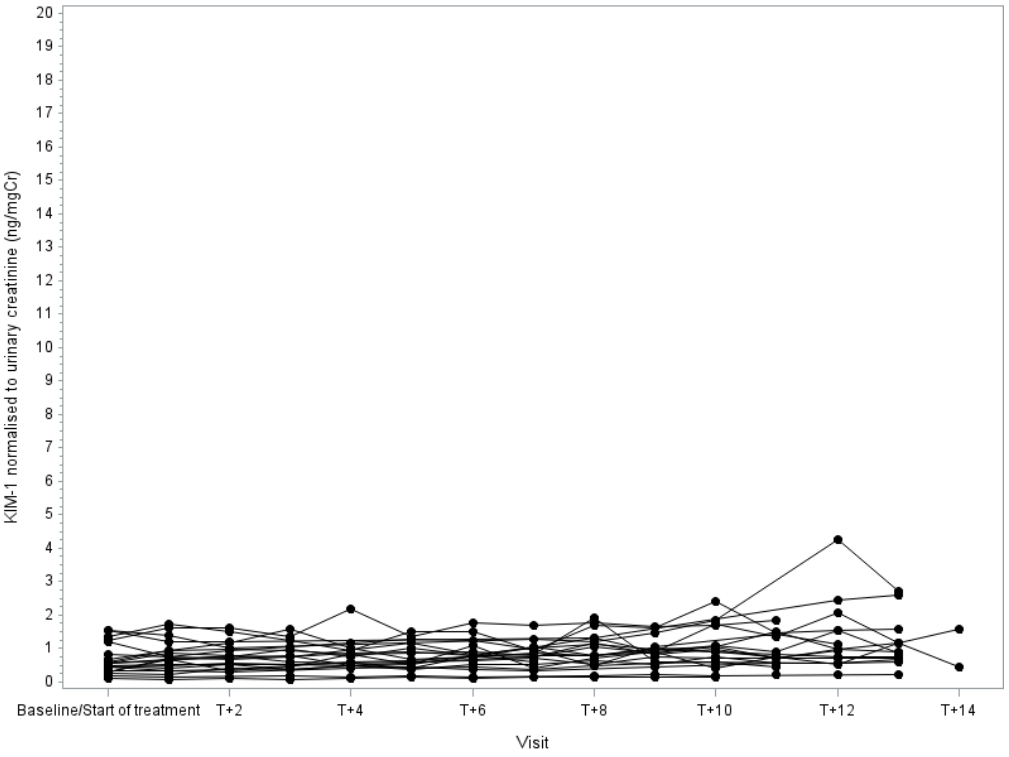
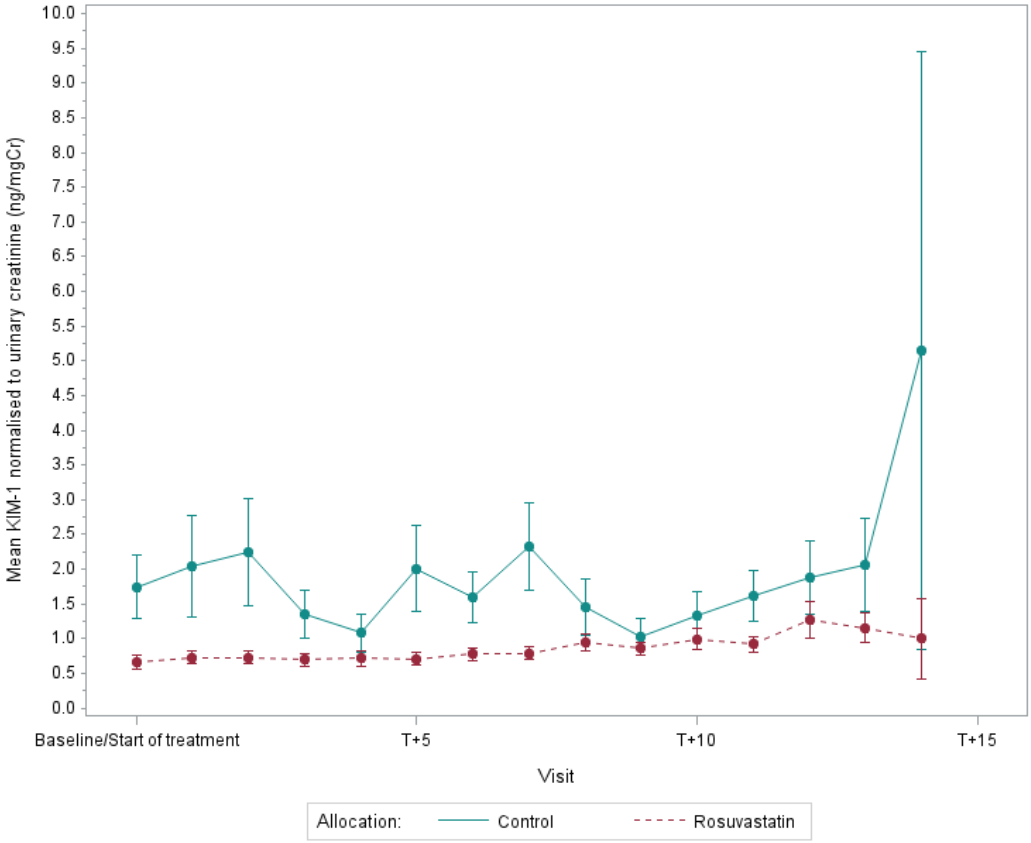


Figure 9.7: KIM-1 Individual Profile Plots: Rosuvastatin group



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – KIM-1 Individual Profile Plots.sas*

Figure 9.8: KIM-1 Mean profile plots



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – KIM-1 Individual Profile Plots.sas*

9.4 Primary Outcome adjusted for age – Post-hoc analysis

The primary outcome analysis was repeated, controlling for age. See Table 9.3 for the results.

Table 9.3: Post-hoc: Primary Outcome adjusted for age: ANCOVA results

Treatment group	N	Estimated geometric mean fold-change of normalised NGAL	Estimated mean treatment difference*	95% CI	P-value
Control	24	1.88	1.03	0.83, 1.29	0.75
Rosuvastatin	20	1.95			

*Adjusted for baseline normalised KIM-1 and age.

Figure 9.9 to Figure 9.11 show the model diagnostics.

Figure 9.9: Histogram assessing normality of residuals for post-hoc analysis of primary outcome adjusted for age

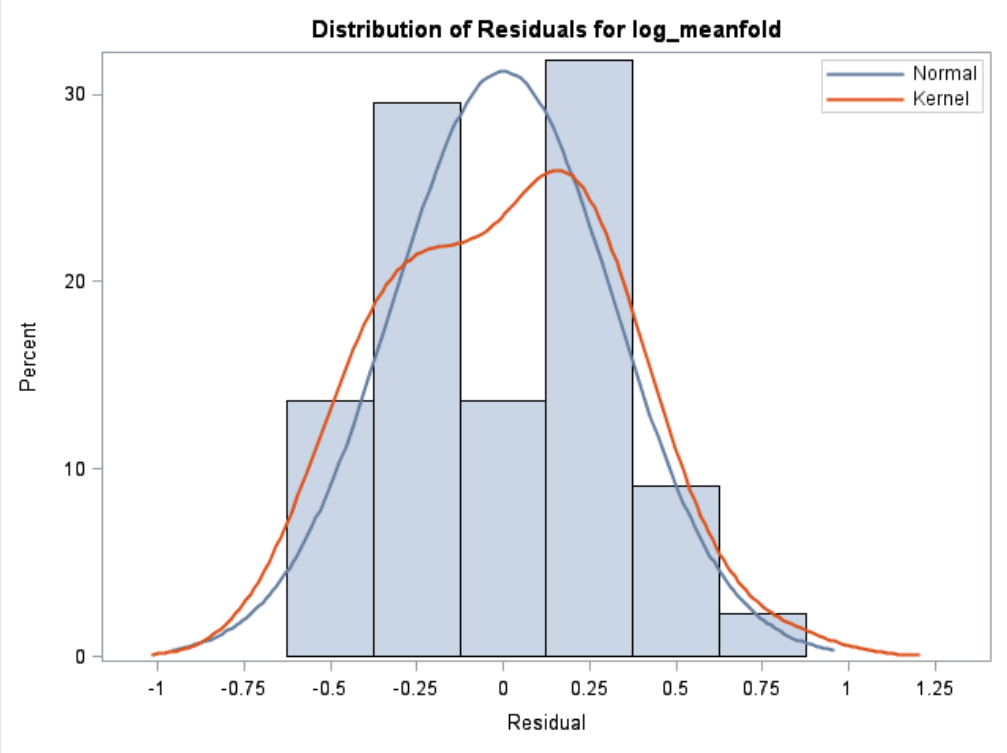


Figure 9.10: Q-Q plot assessing normality of residuals for post-hoc analysis of primary outcome adjusted for age

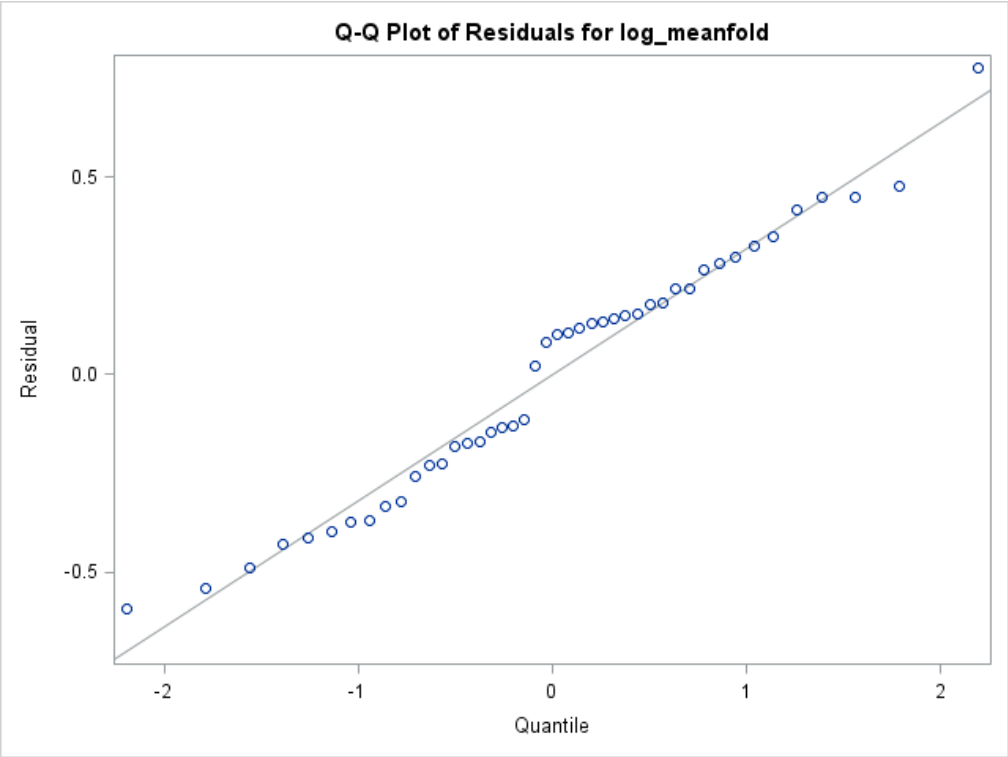
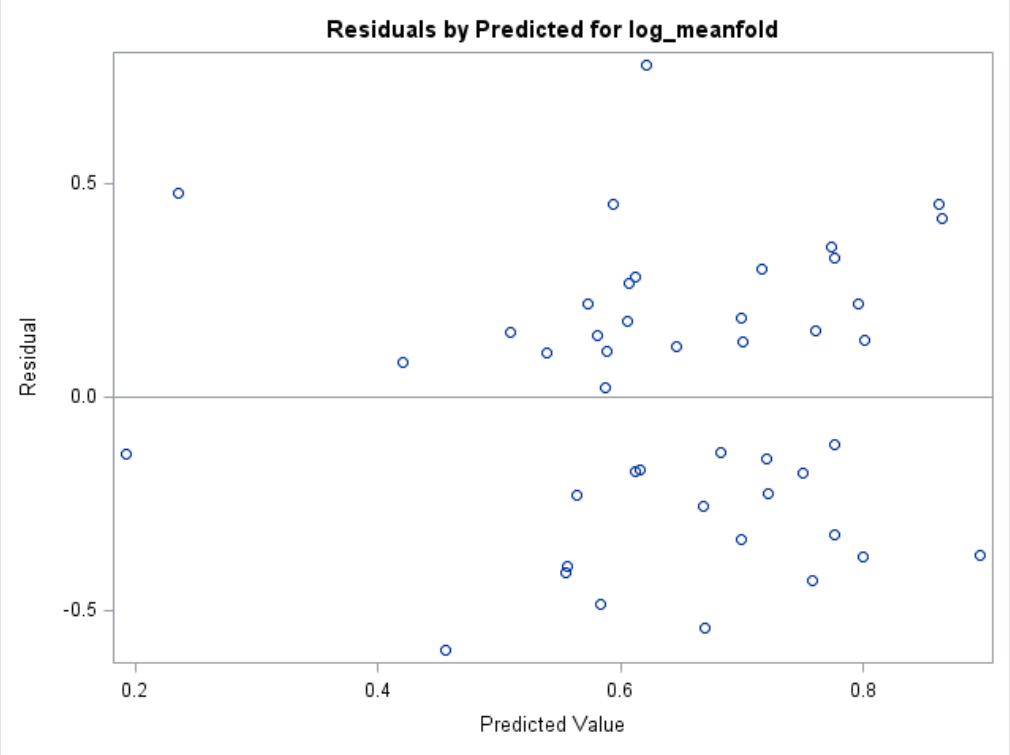


Figure 9.11: Scatter plot of residuals against fitted values assessing homoscedasticity for post-hoc analysis of primary outcome adjusted for age



SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – PO age adjustment.sas*

9.5 KIM-1 changes from baseline to last day of treatment – Post-hoc analysis

Figure 9.12 and Table 9.4 show the change from baseline to final day of treatment in normalised KIM-1.

Figure 9.12: Change in KIM-1 normalised to urinary creatinine from baseline to final day of treatment

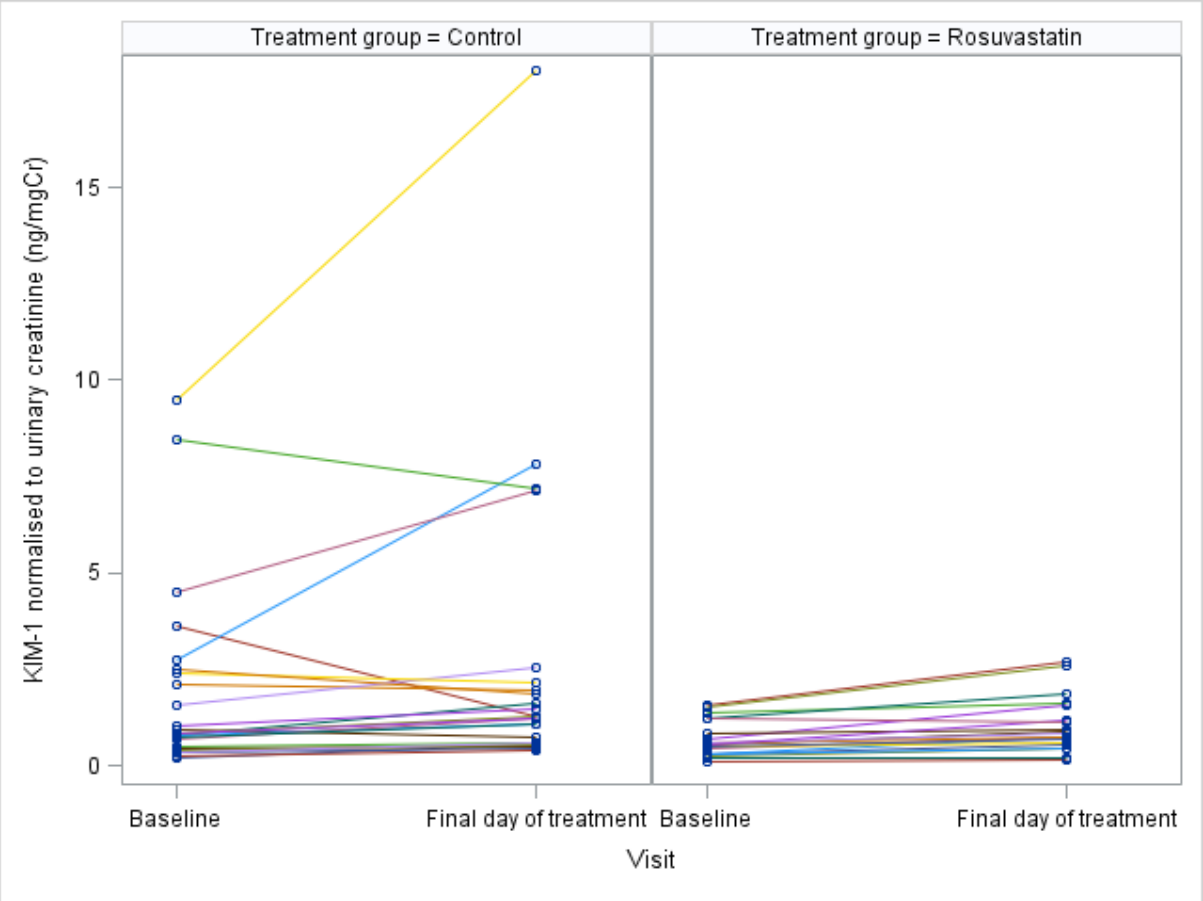


Table 9.4: Number and percentage of participants in each treatment group who had an increase or decrease of KIM-1 from baseline to final day of treatment

Change in KIM-1 from baseline	Control	Rosuvastatin
KIM-1 increased	18 (75%)	19 (95%)
KIM-1 decreased	6 (25%)	1 (5%)
KIM-1 stayed the same	0 (0%)	0 (0%)
Total	**24 (100%)**	**20 (100%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – Overall change in KIM-1.sas*

9.6 NGAL changes from baseline to last day of treatment – Post-hoc analysis

Figure 9.13 and Table 9.5 show the change from baseline to final day of treatment in normalised NGAL.

Figure 9.13: Change in NGAL normalised to urinary creatinine from baseline to final day of treatment

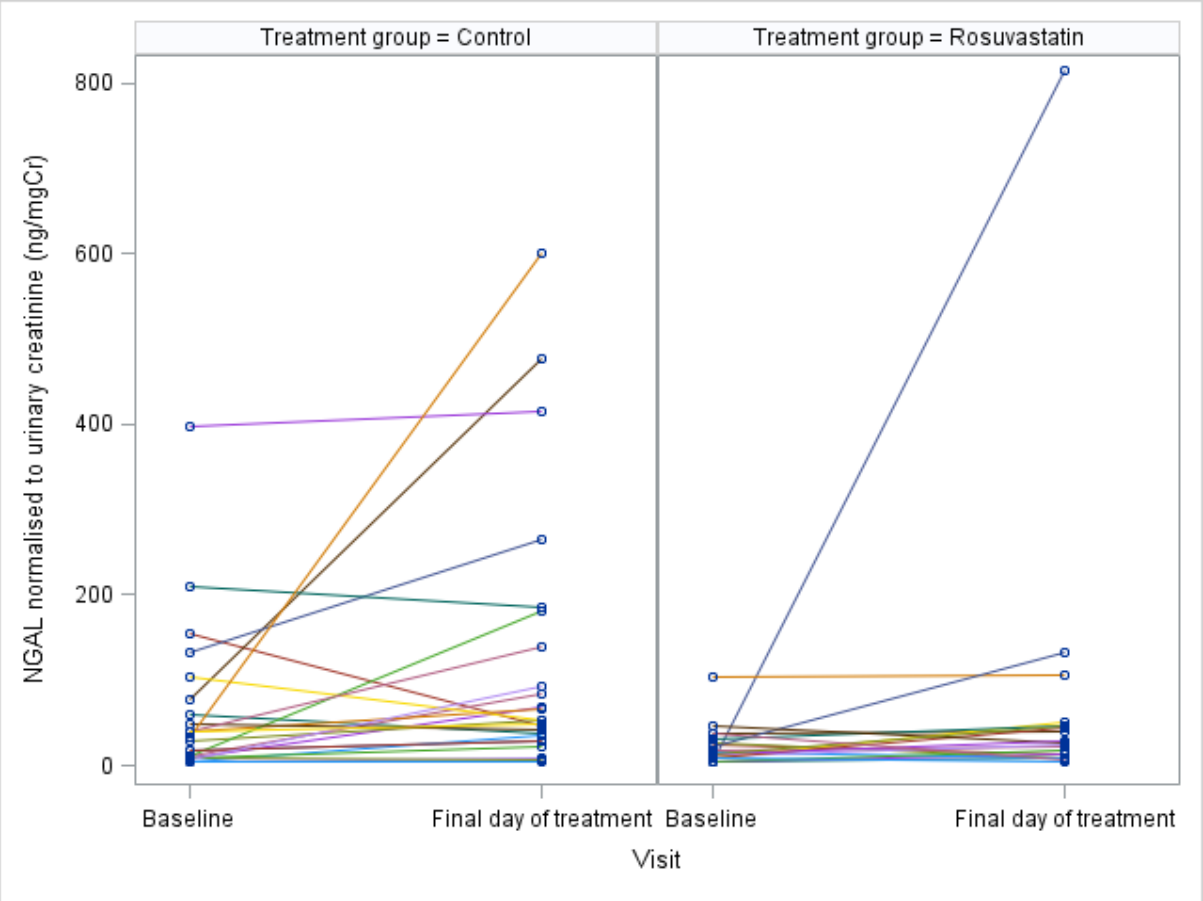


Table 9.5: Number and percentage of participants in each treatment group who had an increase or decrease of NGAL from baseline to final day of treatment

Change in NGAL from baseline	Control	Rosuvastatin
NGAL increased	18 (75%)	14 (70%)
NGAL decreased	6 (25%)	6 (30%)
NGAL stayed the same	0 (0%)	0 (0%)
Total	**24 (100%)**	**20 (100%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\Post-hoc Analysis\PROteKT Final Analysis –Post-hoc – Overall change in NGAL.sas*

9.7 KIM-1 AUC: Sensitivity analysis – Post-hoc analysis

The area under the curve (AUC) of normalised KIM-1 was repeated, excluding any results which were greater than the upper quartile plus 1.5 times the interquartile range (IQR) or lower than the lower quartile minus 1.5 times the IQR. See Table 8.7 for the results.

Table 9.6: KIM-1 AUC: Sensitivity analysis – T-test results

Treatment group	N	Mean (SD) AUC of normalised KIM-1 (ng/mgCr)	Estimated mean treatment difference	95% CI	P-value
Control	23	10.79 (6.66)	0.73	-2.92, 4.38	0.69
Rosuvastatin	21	10.07 (5.31)			

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc – KIM-1 AUC – Sensitivity Analysis.sas*

9.8 NGAL AUC: Sensitivity analysis – Post-hoc analysis

The AUC of normalised NGAL was repeated, excluding any results which were greater than the upper quartile plus 1.5 times the IQR or lower than the lower quartile minus 1.5 times the IQR. See Table 9.7 for the results.

Table 9.7: NGAL AUC: Sensitivity analysis – T-test results

Treatment group	N	Mean (SD) AUC of normalised KIM-1 (ng/mgCr)	Estimated mean treatment difference	95% CI	P-value
Control	27	511.0 (341.6)	94.46	-108.9, 297.9	0.35
Rosuvastatin	21	416.6 (350.4)			

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc – NGAL AUC – Sensitivity Analysis.sas*

9.9 Rosuvastatin levels – Post-hoc analysis

Table 9.8 and Figure 9.14 show the number of participants in the control group who had some level of rosuvastatin in their plasma sample.

Table 9.8: Number of participants in the control group at each time point who had some level of rosuvastatin in their plasma sample

Visit	Number of participants (% of 27)
Baseline	5 (18.52%)
T+1	6 (22.22%)
T+8	3 (11.11%)
T+13/last treatment	2 (7.41%)
Total	**11 (40.74%)**

Figure 9.14: Rosuvastatin levels in the control group

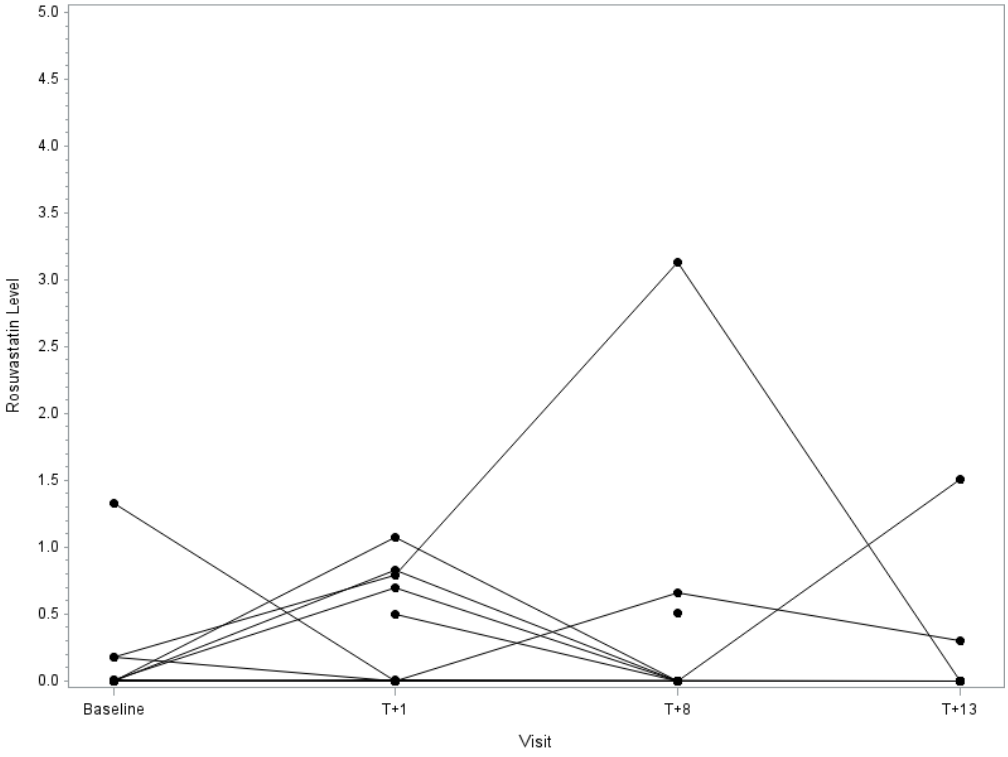


Figure 9.15 shows the level of rosuvastatin for participants in the rosuvastatin group at each time point.

Figure 9.15: Rosuvastatin levels in the rosuvastatin group

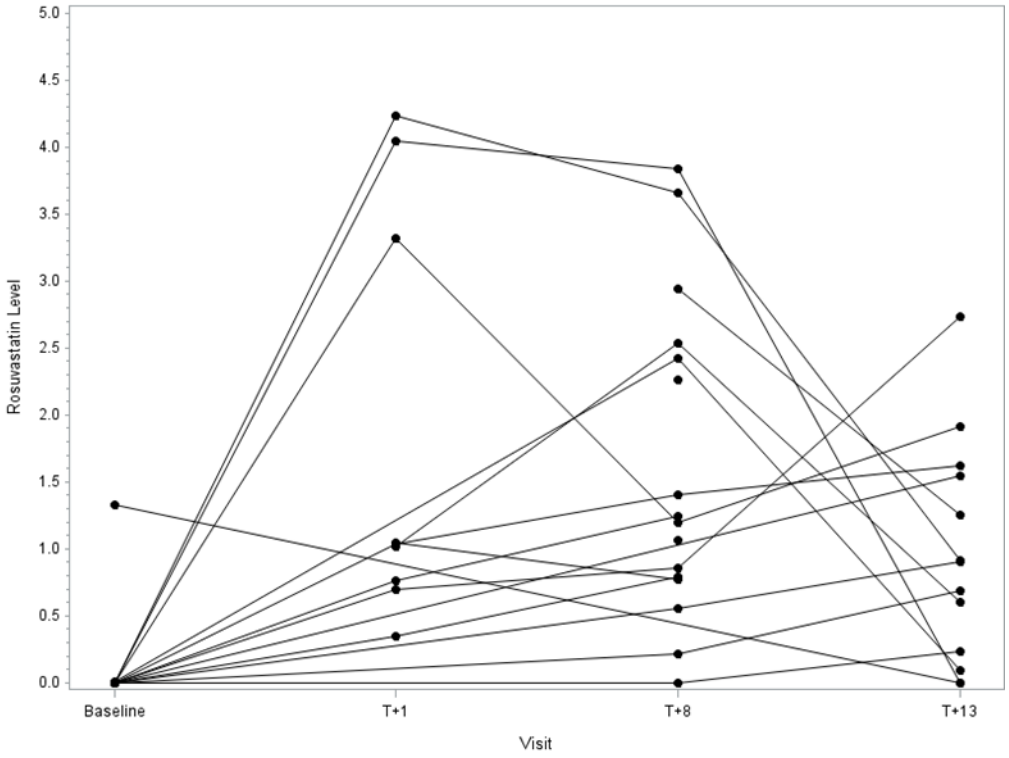


Table 9.9 shows the number of participants in the rosuvastatin group who:

a) Indicated they had taken a rosuvastatin dose in the diary but had a corresponding plasma sample for the same date with a rosuvastatin level equal to 0.

b) Indicated they had taken a rosuvastatin dose in the diary and had a corresponding plasma sample for the same date with a rosuvastatin level greater than 0;

c) Indicated they had **not** taken a rosuvastatin dose in the diary but had a corresponding plasma sample for the same date with a rosuvastatin level greater than 0;

d) Indicated they had taken a rosuvastatin dose in the diary but had a corresponding plasma sample for the same date with a rosuvastatin level equal to 0.

Table 9.9: Rosuvastatin levels for participants in the rosuvastatin arm with a sample and corresponding diary entry

Visit	Number of samples	Number of samples with a corresponding diary entry	Dose taken according to diary and level of rosuvastatin > 0 [a]	Dose not taken according to diary but level of rosuvastatin > 0 [b]	Dose taken according to diary and level of rosuvastatin = 0 [c]
T+1	13	10	10 (100%)	0 (0%)	0 (0%)
T+8	16	15	14 (93.33%)	0 (0%)	1 (6.67%)
T+13/last treatment	10	9	4 (44.44%)	3 (33.33%)	2 (22.22%)
Total	**39**	**34**	**28 (82.35%)**	**3 (8.82%)**	**3 (8.82%)**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc – Rosuvastatin compliance.sas*

9.10 KIM-1 and NGAL reference levels – Post-hoc analysis

Table 9.10 and Table 9.11 show the proportion of participants who were below and above the 95th quantile reference levels [1] for KIM-1 and NGAL, respectively.

Table 9.10: Proportion of KIM-1 normalised to urinary creatinine results which were above the 95th quantile reference levels

Day	Control		Rosuvastatin	
	Below 95th quantile[1]	Above 95th quantile[1]	Below 95th quantile[1]	Above 95th quantile[1]
Baseline	18 (66.67%)	9 (33.33%)	18 (90.00%)	2 (10.00%)
1	19 (70.37%)	8 (29.63%)	18 (90.00%)	2 (10.00%)
2	14 (58.33%)	10 (41.67%)	18 (90.00%)	2 (10.00%)
3	16 (66.67%)	8 (33.33%)	17 (94.44%)	1 (5.56%)
4	16 (69.57%)	7 (30.43%)	15 (88.24%)	2 (11.76%)
5	15 (60.00%)	10 (40.00%)	16 (88.89%)	2 (11.11%)
6	15 (62.50%)	9 (37.50%)	15 (83.33%)	3 (16.67%)
7	10 (50.00%)	10 (50.00%)	18 (94.74%)	1 (5.26%)
8	16 (66.67%)	8 (33.33%)	14 (77.78%)	4 (22.22%)
9	15 (75.00%)	5 (25.00%)	15 (83.33%)	3 (16.67%)
10	16 (76.19%)	5 (23.81%)	12 (75.00%)	4 (25.00%)
11	13 (56.52%)	10 (43.48%)	11 (73.33%)	4 (26.67%)
12	14 (63.64%)	8 (36.36%)	8 (57.14%)	6 (42.86%)
13	8 (53.33%)	7 (46.67%)	9 (75.00%)	3 (25.00%)
14	3 (75.00%)	1 (25.00%)	1 (50.00%)	1 (50.00%)
Total	**208**	**115**	**205**	**40**

[1]*Reference levels are age specific for caucasians; 1 non-caucasian participant was excluded from the summaries*

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc Analysis - KIM-1 cutoffs.sas*

Table 9.11: Proportion of NGAL normalised to urinary creatinine results which were above the 95th quantile reference levels

Day	Control		Rosuvastatin	
	Below 95th quantile[1]	Above 95th quantile[1]	Below 95th quantile[1]	Above 95th quantile[1]
Baseline	24 (88.89%)	3 (11.11%)	20 (100.00%)	0 (0.00%)
1	21 (77.78%)	6 (22.22%)	17 (85.00%)	3 (15.00%)
2	22 (91.67%)	2 (8.33%)	20 (100.00%)	0 (0.00%)
3	21 (87.50%)	3 (12.50%)	18 (100.00%)	0 (0.00%)
4	16 (69.57%)	7 (30.43%)	17 (100.00%)	0 (0.00%)
5	20 (80.00%)	5 (20.00%)	16 (88.89%)	2 (11.11%)
6	18 (75.00%)	6 (25.00%)	16 (88.89%)	2 (11.11%)
7	16 (80.00%)	4 (20.00%)	18 (94.74%)	1 (5.26%)
8	19 (79.17%)	5 (20.83%)	16 (88.89%)	2 (11.11%)
9	16 (80.00%)	4 (20.00%)	16 (88.89%)	2 (11.11%)
10	15 (71.43%)	6 (28.57%)	13 (81.25%)	3 (18.75%)
11	19 (82.61%)	4 (17.39%)	14 (93.33%)	1 (6.67%)
12	16 (72.73%)	6 (27.27%)	12 (85.71%)	2 (14.29%)
13	13 (86.67%)	2 (13.33%)	10 (83.33%)	2 (16.67%)
14	2 (50.00%)	2 (50.00%)	2 (100.00%)	0 (0.00%)
Total	**258**	**65**	**225**	**20**

[1]*Reference levels are gender and age specific for caucasians; 1 non-caucasian participant was excluded from the summaries*

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc Analysis - NGAL cutoffs.sas*

[1] McWilliam SJ et al. Reference intervals for urinary renal injury biomarkers KIM-1 and NGAL in healthy children. Biomarkers in Medicine 2014.

9.11 Serum creatinine increases from baseline – Post-hoc analysis

Table 9.12: Proportion of participants who had a serum creatinine increase of >50% from baseline

Time point	Control		Rosuvastatin	
	Increase from baseline ≤50%	Increase from baseline >50%	Increase from baseline ≤50%	Increase from baseline >50%
T+1	24 (42.11%)	1 (20.00%)	18 (37.50%)	1 (50.00%)
T+8	21 (36.84%)	2 (40.00%)	20 (41.67%)	1 (50.00%)
T+13	12 (21.05%)	2 (40.00%)	10 (20.83%)	0 (0.00%)
Total	**57**	**5**	**48**	**2**

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc Analysis – Serum Creatinine.sas*

Table 9.13: Summary statistics for serum creatinine when corresponding KIM-1 value is above or below the 95th quantile

Time point	KIM-1 above/below 95th quantile	Control				Rosuvastatin			
		N	Mean (SD)	Median (IQR)	Min, Max	N	Mean (SD)	Median (IQR)	Min, Max
T0	Below	18	46.67 (9.98)	45.50 (40.00, 56.00)	30.00, 63.00	18	42.50 (12.48)	41.00 (34.00, 48.00)	28.00, 75.00
	Above	9	41.11 (11.12)	41.00 (31.00, 48.00)	30.00, 62.00	2	49.00 (5.66)	49.00 (45.00, 53.00)	45.00, 53.00
T+1	Below	14	56.57 (25.33)	49.00 (44.00, 55.00)	40.00, 140.00	17	46.65 (12.94)	45.00 (39.00, 59.00)	25.00, 76.00
	Above	8	51.75 (16.22)	49.00 (37.00, 67.00)	33.00, 75.00	1	39.00 (NA)	39.00 (39.00, 39.00)	39.00, 39.00
T+8	Below	11	46.00 (11.02)	44.00 (38.00, 55.00)	32.00, 67.00	17	46.00 (12.60)	47.00 (38.00, 51.00)	26.00, 69.00
	Above	10	50.00 (26.85)	43.00 (30.00, 58.00)	26.00, 114.00	2	41.00 (8.49)	41.00 (35.00, 47.00)	35.00, 47.00
T+13	Below	7	44.00 (9.40)	42.00 (38.00, 46.00)	37.00, 64.00	5	43.00 (12.94)	40.00 (36.00, 53.00)	27.00, 59.00
	Above	6	41.50 (3.94)	40.50 (39.00, 42.00)	38.00, 49.00	4	40.25 (8.22)	38.00 (35.00, 45.50)	33.00, 52.00

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc Analysis – KIM-1 cutoffs.sas*

Table 9.14: Summary statistics for serum creatinine when corresponding NGAL value is above or below the 95th quantile

Time point	NGAL above/below 95th quantile	Control				Rosuvastatin			
		N	Mean (SD)	Median (IQR)	Min, Max	N	Mean (SD)	Median (IQR)	Min, Max
T0	Below	24	44.42 (10.58)	43.50 (35.00,50.00)	30.00, 63.00	20	43.15 (12.04)	42.00 (34.00,49.00)	28.00, 75.00
	Above	3	48.00 (11.36)	53.00 (35.00,56.00)	35.00, 56.00	0	NA	NA	NA
T+1	Below	17	53.76 (24.88)	47.00 (42.00,52.00)	33.00, 140.00	15	44.13 (12.61)	41.00 (36.00,46.00)	25.00, 76.00
	Above	5	58.40 (8.79)	55.00 (54.00,66.00)	48.00, 69.00	3	56.67 (7.57)	60.00 (48.00,62.00)	48.00, 62.00
T+8	Below	16	47.06 (20.52)	43.00 (35.00,53.00)	26.00, 114.00	18	44.67 (11.97)	46.50 (35.00,50.00)	26.00, 69.00
	Above	5	50.60 (18.85)	47.00 (36.00,67.00)	30.00, 73.00	1	60.00 (.)	60.00 (60.00,60.00)	60.00, 60.00
T+13	Below	11	43.36 (7.75)	41.00 (38.00,46.00)	37.00, 64.00	9	41.78 (10.54)	39.00 (36.00,52.00)	27.00, 59.00
	Above	2	40.00 (2.83)	40.00 (38.00,42.00)	38.00, 42.00	0	NA	NA	NA

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\ PROteKT Final Analysis - Post-hoc Analysis - NGAL cutoffs.sas*

9.12 Difference in tobramycin concentrations between rosuvastatin treated group and the control group to identify any pharmacokinetic interaction between rosuvastatin and the tobramycin – Post-hoc analysis

A linear mixed model was fitted to the tobramycin concentration data using a random intercept and adjusting for time since last dose of tobramycin; an interaction between visit and treatment group was included.

Table 9.15: Difference in concentration of tobramycin between the rosuvastatin and control group: Random intercept model results

Time point	Control		Rosuvastatin		Estimated mean treatment difference	95% CI	P-Value	Treatment by time interaction P-value
	N	Estimated mean tobramycin concentration (mg/L)	N	Estimated mean tobramycin concentration (mg/L)				
T+1	23	0.34	18	0.40	0.06	-1.87, 1.99	0.95	0.73
T+8	21	0.45	19	0.58	0.13	-1.82, 2.08	0.90	
T+13/last treatment	16	3.63	16	2.72	-0.91	-3.08, 1.27	0.41	
Overall	**25**	**1.24**	**20**	**1.47**	**-0.24**	**-1.49, 1.02**	**0.70**	

SAS program location: *O:\PROTEKT\Statistical Analysis\Final analysis\Analysis\Programs\PROteKT Final Analysis – Post-hoc Analysis\PROteKT Final Analysis - Post-hoc Analysis – Change in tobramycin.sas*

Appendix 1: Mapping report contents to SAP

This report has been created following the PROteKT Statistical Analysis Plan V4.0 (dated 28/03/2018).

The following table lists each item (tables, figures and section when applicable) in this report and maps each to the relevant SAP section that describes the methods used to compute it.

Section/subsection of SAP	Item within report
Section 15. Disposition of participants	Table 4.1: Summary of randomisation problems Table 5.1: Screening summary by site Table 5.2: Reason(s) for ineligibility Table 5.3: Reasons for non-consent Table 5.4: Recruitment summary by site Figure 3.1: CONSORT diagram Figure 5.1: Recruitment Graph
Section 15.2. Post randomisation discontinuations	Table 6.11: Premature treatment discontinuation
Section 16. Protocol Deviations	Table 6.2: Data sets analysed Table 6.3: Protocol deviations Table 6.4: Protocol deviations split by site Table 6.5: Overall protocol deviations by site
Section 18.2. Demographic and Other Baseline Characteristics	Table 6.1: Baseline Characteristics
Section 18.3. Compliance with treatment	Table 6.10: Returned diaries Table 6.12: Tobramycin compliance Table 6.13: Tobramycin compliance – Overall summary statistics by site Table 6.14: Tobramycin compliance – Control group summary statistics by site Table 6.15: Tobramycin compliance – Rosuvastatin group summary statistics by site Table 6.16: Rosuvastatin compliance line listing Table 6.17: Rosuvastatin compliance – Summary statistics by site
Section 18.4. Analysis of Primary Outcome	Table 8.1: Primary Outcome – Primary efficacy assessment ANCOVA Results Figure 8.1: Histogram assessing normality of residuals Figure 8.2: Q-Q plot assessing normality of residuals Figure 8.3: Scatter plot of residuals against fitted values assessing homoscedasticity Table 8.2: Primary Outcome – Sensitivity Analysis 1: ANCOVA Results Table 8.3: Primary Outcome – Sensitivity Analysis 2: ANCOVA Results Table 8.4: Primary Outcome – Sensitivity Analysis 3: ANCOVA Results
Section 18.5. Analysis of Secondary Outcomes	Table 8.8: Difference in serum concentration of creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results

Section/subsection of SAP	Item within report
	Table 8.10: Difference in serum concentration of eGFR during tobramycin exposure between the rosuvastatin and control group: Random intercept model results Table 8.12: Difference in NGAL normalised to urinary creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results Table 8.17: Difference in FEV1 during tobramycin exposure between the rosuvastatin and control group: Random intercept model results Table 8.19: Difference in CRP during tobramycin exposure between the rosuvastatin and control group: Random intercept model results Table 8.21: Rosuvastatin concentrations and their corresponding KIM-1 values at each time point Figure 8.4: Histogram assessing normality of residuals for sensitivity analysis 1 Figure 8.5: Q-Q plot assessing normality of residuals for sensitivity analysis 1 Figure 8.6: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 1 Figure 8.7: Histogram assessing normality of residuals for sensitivity analysis 2 Figure 8.8: Q-Q plot assessing normality of residuals for sensitivity analysis 2 Figure 8.9: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 2 Figure 8.10: Histogram assessing normality of residuals for sensitivity analysis 3 Figure 8.11: Q-Q plot assessing normality of residuals for sensitivity analysis 3 Figure 8.12: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 3 Figure 8.13: Panel of residual statistics for sensivity analysis 4: Random intercept for centre model Figure 8.14: Histogram assessing normality of residuals for sensitivity analysis 5 Figure 8.15: Q-Q plot assessing normality of residuals for sensitivity analysis 5 Figure 8.16: Scatter plot of residuals against fitted values assessing homoscedasticity for sensitivity analysis 5 Figure 8.17: Individual profile plots of serum creatinine – control group Figure 8.18: Individual profile plots of serum creatinine – rosuvastatin group Figure 8.19: Mean profile plots of serum creatinine by treatment group Figure 8.20: Individual profile plots of serum eGFR – control group Figure 8.21: Individual profile plots of serum eGFR – rosuvastatin group Figure 8.22: Mean profile plots of serum eGFR by treatment group Figure 8.23: Individual profile plots of NGAL – control group Figure 8.24: Individual profile plots of NGAL – rosuvastatin group Figure 8.25: Mean profile plots of NGAL by treatment group Figure 8.26: Histogram assessing normality of residuals of NGAL ANCOVA model Figure 8.27: Q-Q plot assessing normality of residuals of NGAL ANCOVA model Figure 8.28: Scatter plot of residuals against fitted values assessing homoscedasticity of NGAL ANCOVA model Figure 8.29: Histogram assessing normality of residuals for NGAL sensitivity analysis Figure 8.30: Q-Q plot assessing normality of residuals for NGAL sensitivity analysis Figure 8.31: Scatter plot of residuals against fitted values assessing homoscedasticity for NGAL sensitivity analysis Figure 8.32: Individual profile plots of FEV1 – control group Figure 8.33: Individual profile plots of FEV1 – rosuvastatin group

Section/subsection of SAP	Item within report
	Figure 8.34: Mean profile plots of FEV in 1 second by treatment group Figure 8.35: Individual profile plots of CRP – control group Figure 8.36: Individual profile plots of CRP – rosuvastatin group Figure 8.37: Mean profile plots of CRP by treatment group Figure 8.38: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+1 Figure 8.39: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+8 Figure 8.40: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to T+13 Figure 8.41: Scatterplots of rosuvastatin concentrations against reduction in KIM-1 normalised to urinary creatinine from baseline to 4 weeks following treatment cessation
Section 19. Missing data and withdrawals	Table 6.6: Withdrawal from follow-up Table 6.7: Line listing of samples collected Table 6.8: Missing primary outcome data by site Table 6.9: Line listings of participants with missing baseline urine samples
Section 20. Additional Analyses	Table 8.5: Primary Outcome – Sensitivity Analysis 4: Random Intercept for Centre Mixed Model Results Table 8.6: Primary Outcome – Sensitivity Analysis 5: ANCOVA results Table 8.7: Primary Outcome – Additional Analysis: AUC T-test results Table 8.9: Sensitivity Analysis: Difference in serum concentration of creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers Table 8.11: Sensitivity Analysis: Difference in serum concentration of eGFR during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers Table 8.13: Sensitivity Analysis: Difference in NGAL normalised to urinary creatinine during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers Table 8.14: NGAL – Change from baseline to peak: ANCOVA Results Table 8.15: NGAL – Sensitivity Analysis: ANCOVA results Table 8.16: Additional Analysis: NGAL AUC T-test results Table 8.18: Sensitivity Analysis: Difference in FEV1 during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers Table 8.20: Sensitivity Analysis: Difference in CRP during tobramycin exposure between the rosuvastatin and control group: Random intercept model results – Removal of outliers
Section 21. Safety Evaluations	Table 7.1: Adverse reactions Table 7.2: Adverse reactions by severity Table 7.3: Adverse reactions by relatedness Table 7.4: Serious Adverse Events